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VOLUME 100 — APRIL 1991
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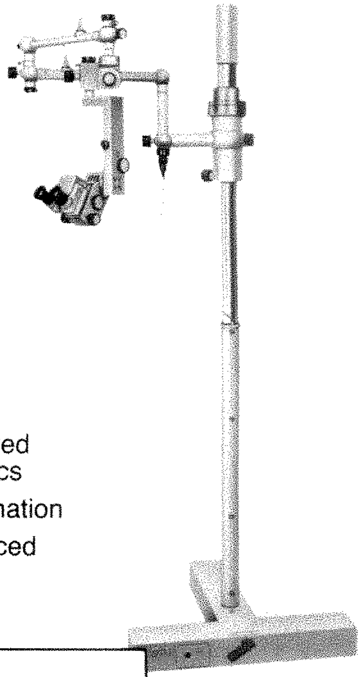

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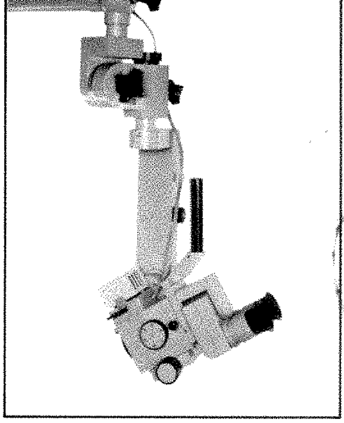

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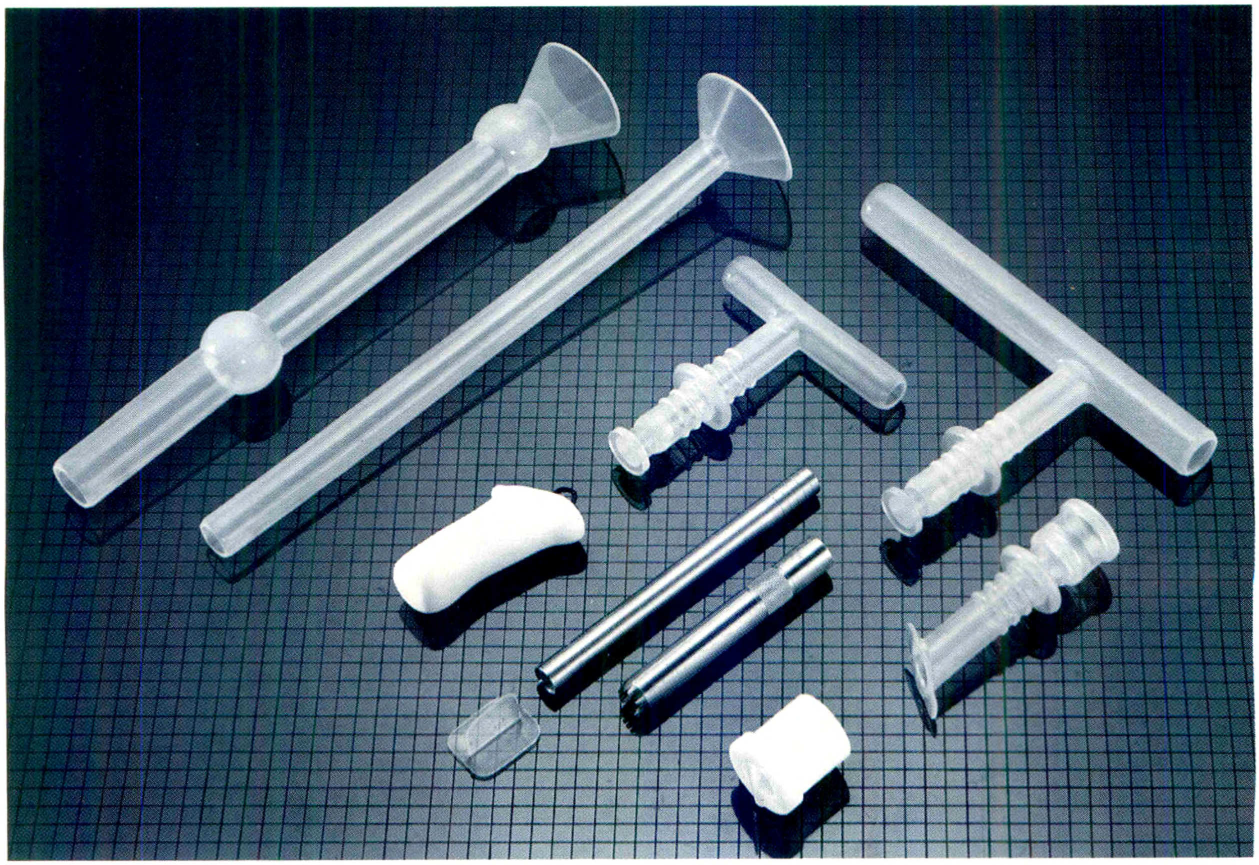

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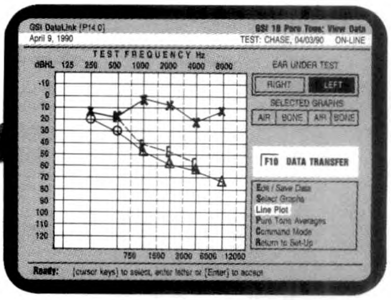
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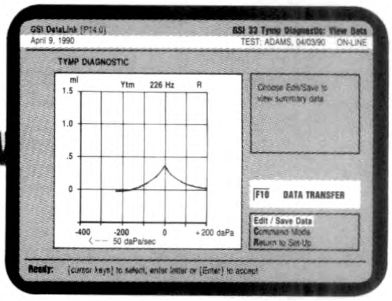
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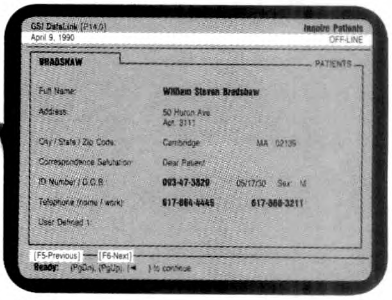
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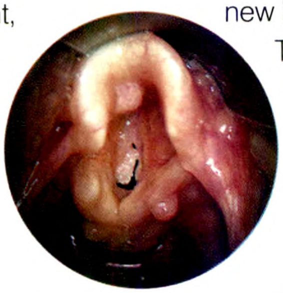

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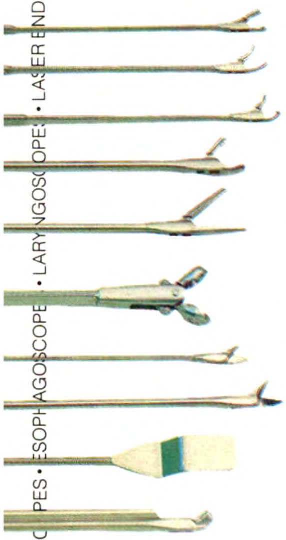

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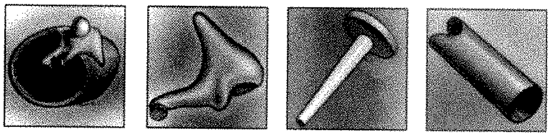

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ANNALS OF HEAD & NECK MEDICINE & SURGERY®

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ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY (ISSN 0003-4894) is published monthly by Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108. Second-class postage paid at St Louis, Mo. POSTMASTER: Send address changes to Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108.

Printed on acid-free paper

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Ann Otol Rhinol Laryngol 100:1991

SIXTEENTH DANIEL C. BAKER, JR, MEMORIAL LECTURE

SURGICAL MANAGEMENT OF SUPRAGLOTTIC CANCER AND ITS LYMPH NODE METASTASES IN A CONSERVATIVE PERSPECTIVE

ETTORE BOCCA, MD
MILAN, ITALY

Supraglottic laryngectomy combined with functional elective or curative neck dissection is a priceless contribution toward treatment of supraglottic cancer and its lymph node metastases. The history and background of this conservative approach is reviewed. Results related to staging are presented. Irradiation as a combined or alternative therapy is considered.

KEY WORDS — neck dissection, supraglottic cancer, supraglottic laryngectomy.

Whenever, in less recent years, I happened upon any of our former supraglottic patients, with their permanent tracheostomy, drooping shoulders, and a shirt collar much too large for an exceedingly thin neck, surmounted by an apparently disproportionately big head, I felt unwillingly guilty for having inflicted upon them such a disabling and unnecessary mutilation. Even more so, if one considers that carcinoma of the supraglottis has a heavy incidence in the total number of laryngeal cancers, and that it affects patients at a relatively young age, at their peak of social and economic activity.

Until 1950, traditional total laryngectomy, often combined with radical neck dissection, was the only accepted surgical measure. It resulted in a most severe and socially devastating disability. The story of horizontal supraglottic laryngectomy started with the masterwork of Baclesse,[1] *Tumeurs Malignes du Pharynx et du Larynx*, in which the radiographic diagnosis of these tumors was thoroughly described. It was clearly stated that supraglottic cancer does not invade the glottis.

These observations certainly inspired Justo Alonso[2-5] of Uruguay when he conceived the possibility of guiding the surgeon's knife to follow the barriers nature had erected against tumor invasion. The official year of birth of supraglottic laryngectomy is 1947. In that year, Alonso[2] presented his early experience before the American Academy of Ophthalmology and Otolaryngology, followed by the better-elaborated reports of 1951,[3] 1957,[4] and 1975.[5] But the time was not ripe for this idea to be accepted, as it seemed to upset the traditional and deeply rooted principles of cancer surgery.

In the mid-1950s Sanchez Rodriguez[6] in Spain, Leroux Robert[7-9] in France, and Ogura et al[10-12] and Som[13,14] in the United States started taking an interest in partial supraglottic laryngectomy; however, their first approaches were fairly timid, with no clear-cut indications. They had no followers for many years. In 1953 I published the results of the observations made on 150 operative specimens of total supracricoid laryngectomies performed for supraglottic cancer.[15] The conclusion was that primary cancer of the supraglottis spreads onward to the preepiglottic space, and upward to the epilarynx, but never downward. Whatever the size of the cancer, the glottis shows no sign of invasion. These findings were repeatedly confirmed later, especially in the fundamental works of Kirchner et al[16-18] and Micheau et al.[19]

In spite of these findings, and in spite of the fact that Alonso visited our clinic in Milan in 1953 and performed supraglottic laryngectomy on two patients who were alive and well many years later, I could not persuade my chief at that time, Prof L. Pietrantoni, to accept this surgery. Surprisingly enough, I concluded the aforesaid observations by stating that they could not justify conservative surgery in supraglottic cancer. Until 1960 this type of surgery had only been accepted in Uruguay, Spain, and Argentina; elsewhere it was looked at with extreme caution, or it was accepted for most limited indications.

About 1955, I started hiding from my chief some patients with supraglottic cancer whom I submitted surreptitiously to supraglottic surgery. The first results on 30 cases with 3- to 5-year follow-up were reported at the French Congress in 1960 and published in 1961,[20] after the death of my chief. I began with routine supraglottic surgery in 1961, and I was surprised to see that despite my late start, I found myself among its few pioneers in Europe and overseas. By the 1970s the operation was extensively practiced in Spain and Italy and less commonly in France, but it was still far from being popular in

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From the Department of Clinical Otolaryngology, University of Milan, Milan, Italy.

Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

REPRINTS — Ettore Bocca, MD, Viale Regina Giovanna, 15, 20129 Milan, Italy.

TABLE 1. BACKGROUND OF SUPRAGLOTTIC LARYNGECTOMY

Anatomic evidence	Supraglottis and glottis have different embryologic derivations and different and separate lymphatic networks
Pathologic evidence	Supraglottic tumor nerve invades glottis, regardless of its size; its forward extension is contained within preepiglottic space
Clinical evidence	Comparative results of supraglottic and total laryngectomy in vestibular cancer show no significant difference

Germany, northern and eastern Europe, England, and the United States.

It may be of interest to read this commentary: "The effort of conserving laryngeal structures appears to challenge the concept of a wide margin of tissue. To quote one foremost surgeon, a 1-mm margin was preserved around the tumor mass. Failure to encompass the lesion would increase in this type of brinkmanship but their reports assume that this is not the case. Let us hope that lesser surgeons will have the same happy results."[21] Yet the background of supraglottic surgery had long been set (Table 1). Today, some residual resistance may still be identified in the frequency of unjustified restrictions to the indications, or of alternative and often less effective therapies, or of some untoward attempts at technical compromises. In the opposite direction, overenthusiasm has caused many a disaster because of faulty indications or faulty technique.

Whenever the tumor is located primarily in the infrahyoid portion of the supraglottis, the line of resection may be extremely close to its limits because of the well-known presence of unfranchisable barriers inferiorly and anteriorly; enough healthy tissue separates the tumor superiorly from the epilaryngeal margins. On the other hand, the resection must respect a wide margin of healthy tissue beyond the laryngeal margins when the tumor is located primarily in the epilarynx or invades the epilarynx extensively from below. However, even in these cases the sacrifice of the glottis is scarcely justified; an extended supraglottic laryngectomy may be performed with but a few added risks. A portion of the tongue, one of the arytenoids with the exception of its vocal process, and a lesser or greater portion of the pyriform fossa will be included in the surgical resection, separately or in combination.[22-24]

It cannot be overstressed that the supraglottis is a cancerological unit: it must be resected in its entirety whatever the site of origin of cancer within its boundaries. Quite a few exceptions may be admitted for unusual conditions; for these, no definite rules can be given, the decision being made in a particular case on the basis of large experience.[23]

TABLE 2. TNM CLASSIFICATION OF SUPRAGLOTTIC CANCER

	N0	N1	N2	N3	Total
T1	47	16	0	0	63
T2	252	92	20	3	367
T3	62	35	8	2	107
Total	361	143	28	5	537

Data from references 25 and 26.

TABLE 3. TNM DISTRIBUTION AND STAGING OF SUPRAGLOTTIC CANCER

Stage I	47 (8.75%)	T1N0	47
Stage II	252 (46.92%)	T2N0	252
Stage III	205 (38.18%)	T1N1	16
		T2N1	92
		T3N0	62
		T3N1	35
Stage IV	33 (6.15%)	T2N2	20
		T2N3	3
		T3N2	8
		T3N3	2
Total	537 (100%)		537

Data from references 25 and 26.

Our data from the years 1961 through 1987 are reported in Tables 2 to 5[22,24-26] and show very little variation from those published in the previous years. These data have now been largely confirmed from different sources in the available literature. This extended type of supraglottic laryngectomy should be more often resorted to for added security in doubtful cases.

Supraglottic laryngectomy may be defined as a turning point in the surgery of cancer of the larynx, the most important progress since Billroth's[27] laryngectomy of 1873. It is much safer than many other conservative procedures. However, it offers the solution to only half the problem, the other half consisting of the regional lymph node metastases frequently observed clinically or histologically. Therefore, classic neck dissection in continuity was more and more often effected with its burden of disability, complications, or sequelae,[28] in sharp contrast with the full restoration of function afforded by supraglottic laryngectomy. It became even less acceptable when local conditions commanded that it be effected bilaterally. Said Maxwell Ellis in 1966 (personal communication), "Bilateral radical neck dissection is a most disabling operation. I find this problem almost insoluble every time I meet it." These words have not lost their value. About 1960, Suarez,[29,30] both a fine anatomist and a fine otolaryngologist, introduced his functional neck dissection. Unfortunately, he never described it in detail, and it might have remained largely ignored but for

TABLE 4. RECURRENCES AFTER SUPRAGLOTTIC AND EXTENDED SUPRAGLOTTIC LARYNGECTOMY

		Local		*Neck*		*Total*	
Stage	*N*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	47	3	6.38	1	2.12	4	8.50
II	252	46	18.25	8	3.17	54	21.42
III	205	40	19.52	19	9.26	59	28.78
IV	33	11	33.33	6	18.18	17	51.51
Total	537					134	(24.95%)

Data from references 24-26.

TABLE 5. SUPRAGLOTTIC LARYNGECTOMY (537 CASES FROM 1961 TO 1987)

	Recurrence Rate	*5-Year Cure Rate*
Standard supraglottic laryngectomy (380 cases)	76 (20%)	80%
Visceral	47	
Neck	29	
Extended supraglottic laryngectomy (107 cases)	29 (27%)	73%
Visceral	24	
Neck	5	
All cases (standard and extended; 487 cases)		78%

Data from references 22 and 24-26.

the privilege I had of observing it in the operating theater in 1962.

The philosophy of functional neck dissection closely resembles that of supraglottic laryngectomy in the sense that the surgeon's knife must respect the limits nature has set to tumor invasion. Its anatomic basis may be traced back in the precious but hardly known little books of Sebileau[31] and Truffert[32] published by Masson (Paris) in the early 1920s. Here a totally new description of the lateral spaces of the neck is presented, quite different from the descriptions of the traditional textbooks of human anatomy. According to Truffert's description, these spaces appear to be divided into well-sealed major aponeurotic compartments formed by the interconnections between muscular and vascular aponeuroses. They contain all the celluloadipose tissue together with the whole lymphatic repository of the neck. This fundamental idea was further developed by Suarez,[29,30] who translated an anatomic reality into a surgical opportunity. Thus, the background of functional neck dissection was firmly set (Table 6). The concepts of Truffert and Suarez were further elaborated by Pernkopf,[33] Bocca et al,[34-40] Calearo and Teatini,[41,42] and Teatini and Zampano[43] and led to the establishment of a uniform and well-regulated surgical technique.

Nevertheless, what had happened with supraglottic laryngectomy repeated itself with functional neck dissection: it was nearly unanimously condemned, as challenging the principles of radicality. The following is but one of many unfavorable comments: "Several partial neck dissections have been described: among them a functional neck dissection. They do not appear to be a safe procedure and are not recommended."[44] Others oppose functional neck dissection on the grounds that it is a difficult operation. Surely, it is a different operation from classic (radical) neck dissection. It cannot be invented or improvised: it requires hours of training on the dissection table and in the operating theater. After that, it is a piece of precise surgery, by no means difficult and highly gratifying, if one adheres strictly to its well-defined anatomic rules. As with supraglottic laryngectomy, failure to grasp the essence of the operation led to unduly restricted indications, or to alternative therapeutic choices such as irradiation, or to untoward technical compromises often resembling plucking a plum from a cake rather than a neck dissection.

TABLE 6. BACKGROUND OF FUNCTIONAL NECK DISSECTION

Anatomic evidence	Aponeurotic compartments may be easily separated from muscles and vessels that they envelop, but to which they bear no other relationship than that of close vicinity
Pathologic evidence	If lymph node capsule remains intact, metastatic cancer always remains within boundaries of aponeurotic compartments
Clinical evidence	Comparative results of functional versus classic (radical) neck dissection do not show significant difference

TABLE 7. RECURRENCE RATE OF FUNCTIONAL VERSUS CLASSIC NECK DISSECTION

	No. of Cases	*Recurrences*	
		No.	*%*
Elective neck dissection			
Functional	672	16	2.38
Classic	226	15	6.63
Curative neck dissection			
Functional	171	52	30.4
Classic	188	90	47.9

Data from reference 39.

It is my opinion that functional neck dissection is a turning point, the most important progress in surgery of the neck since Crile's[45] description. It completes the conservative perspective of the surgical management of supraglottic cancer and its lymph node metastases. It offers the answer to the long-debated question as to whether or not an elective neck dissection should be performed routinely in high-risk cases, and it offers the solution to the distressing dilemma of whether or not a curative neck dissection should be effected on both sides.

I had the unique occasion for an important retrospective study of the material accumulated by the same surgical team or part of it, working with the same technique, following the same principles, and using the same methods of classification and analysis of results. This study covers a period of 30 years and is divided into two parts: the first refers to the years from 1948 to 1960, a period in which only classic (radical) neck dissection, elective or curative, was performed. The second refers to the years from 1961 through 1979, a period in which only functional neck dissection was performed.

A comparison between the number of recurrences in the two periods was made. Of course, for both series, the comparison concerns only N0, N1, and N2 cases, N3 cases being a contraindication to functional neck dissection (Table 7[39]). A distinct improvement in results in the period from 1961 to 1979 is evident. These figures, already published in 1984,[39] show no significant changes from those subsequently collected by former members of my staff.[41-43] The improvement certainly does not depend on greater radicality of functional neck dissection as against classic (radical) neck dissection, but upon the fact that the number of bilateral dissections, elective or curative, increased from 30% in the first period to 90% in the second period, thus preventing neck recurrences in the untreated side of the neck.

Since we started, in 1962, the combined routine conservative surgical approach to supraglottic cancer and its tributary lymphatic territories, we were rewarded with a most gratifying 5-year cure rate, possibly the highest in the available literature (Table 5).

Some may object that this practice led to a number of "blank" or useless elective neck dissections; this is really the case in about 70% of cases. For this reason a wait-and-see attitude is often preferred. The need for a more accurate prevision of occult metastasis has long been felt. We also published an attempt[46] to predict their presence on the basis of clinical and pathologic parameters, whose significant favorable coincidence only occurred in less than 2% of cases. None of the other methods proposed has proved to be more reliable so far. Nor does computed tomography or magnetic resonance imaging seem to afford better preliminary information. Until progress in the experiments with labeled antibodies affords the possibility of detecting small groups of cancer cells nested in the lymph nodes, the clinical value of functional elective neck dissection in high-risk cases does not need to be reconsidered on the basis of available data. No death from cancer that elective neck dissection could have avoided is ethically justified.

Furthermore, if we want to consider elective functional neck dissection in continuity with supraglottic laryngectomy under the aspect of risks and costs, it does not add to morbidity or to the operative risks, and it avoids the extra costs of routine computed tomography or magnetic resonance imaging. At this point a question arises. Why not renounce surgery altogether in favor of radiotherapy both on the primary and on the neck? This choice has had and still has many advocates in the United States, so the question merits a response, although some may presume that it is biased by my being a surgeon.

Thanks to the steady progress of irradiation weapons and to improved models of fractioning the daily doses, the radiotherapy of today may claim results that are very close to those of surgery in supraglottic cancer, in T1N0 stage I cases.[47-51] They are even better in primitive epilaryngeal growths, especially at the cross point of the three folds. However, the results show a progressive discrepancy in favor of surgery from stage II through stage IV. This has been our conclusion, arrived at in a combined retrospective study, unpublished so far, made in common by the same surgeon and the same radiotherapist over a period of 20 years and concerning 800 cases of supraglottic cancer, classified and staged in common, of which 500 had been submitted to surgery and 300 to radiotherapy. These conclusions have been repeatedly confirmed in the literature.

It must be said that even under such favorable circumstances as in our case, comparison is always extremely difficult for several reasons: 1) a difference in staging, 2) different definitions of success and failure depending on whether only T or both T and N are considered, and 3) different classification of patients cured by salvage procedures or irradiation.

In the choice of treatment the following factors play a decisive role.

1. Will of the patient.
2. Patient's general and pulmonary conditions.
3. Site and stage of the tumor.
4. Increased risk of second tumors.
5. Risk of secondary cancer induced by irradiation.
6. Risk of permanent radiation tissue damage.
7. Greater risks with salvage surgery.
8. Difficulty of detecting early recurrences in an irradiated larynx.
9. Greater frequency of late recurrences after radiotherapy.
10. Expertise of the surgeons and of the radiation oncologist.

Once the choice is made between surgery and radiotherapy,[52,53] it must be a matter of all or none. Whatever the choice is, control of cancer is expected to follow each one of the selected treatments. Combined surgery and radiotherapy has infrequent indications and does not appear to improve the results. This holds true both for preoperative and postoperative irradiation, whenever radical surgery is feasible or actually accomplished.

There are, of course, some exceptions. Preoperative irradiation of the neck may be recommended for large fixed nodes apparently beyond the limits of surgery. Postoperative irradiation of the neck is recommended in all cases of demonstrable capsular rupture. Last, a multidisciplinary approach will be attempted in virtually lost cases. Apart from these exceptions, I do not recommend postoperative irradiation of the neck as a substitute for functional elective neck dissection. Likewise, I do not recommend postoperative irradiation of the larynx after supraglottic laryngectomy. It means doubtful radicality, a consequence of faulty technique or faulty indications. Furthermore, it may create functional problems. I do not recommend topographically combined treatment, ie, irradiation of the primary and surgery on the neck. It seems disputable and time-consuming if a conservative surgical procedure may be effected on both fields in a single session.

Routine indiscriminate postoperative wide-field irradiation of the primary and neck may cut off the road to selective and successful narrow-field irradiation should a localized recurrence appear. Burning bridges is not a wise policy.

I do not take into consideration routine radical irradiation plus salvage surgery any more than routine radical surgery plus salvage irradiation. This is just leaving others the bones after eating the meat. Not all supraglottic cancers do equally well with surgery or radiotherapy: a wise choice averts failures requiring often unsuccessful salvage treatments.

I conclude by saying that many things have changed in the surgical management of supraglottic cancer, but changes concern the techniques and not the principles of cancer surgery, that is, the necessity of being radical in both the primary and the neck. Supraglottic laryngectomy combined with functional elective or curative neck dissection is fully in line with those principles and it represents a priceless contribution to saving more lives while sparing mutilation. On the other hand, it is the only acceptable response to the growing challenge of radiotherapy: surgery respects function and body image, affords a more effective regional control of cancer, allows a deeper insight into the physiopathology of cancer invasion, is a precious guide to our clinical behavior and to more accurate prognosis, is better tolerated, and avoids harmful local and general biologic effects. I am persuaded that the solution to the problem of supraglottic cancer in its entirety is still in the surgeon's hands, provided that we remember that we are waging a war against cancer in the larynx and in the lymph nodes of the neck, and not against the larynx and the neck.

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Ann Otol Rhinol Laryngol 100:1991

ROLE OF PARTIAL LARYNGECTOMY AFTER IRRADIATION IN THE TREATMENT OF LARYNGEAL CANCER: A VIEW FROM THE UNITED KINGDOM

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This retrospective study evaluates the use of conservation surgical salvage techniques in cases of early (T1 and T2) laryngeal cancer after full-dose external irradiation. Fifty patients in one London hospital and 68 patients in another were studied for the period 1963 to 1988. Treatment policy directed that the majority of limited glottic and supraglottic tumors should be treated initially by external irradiation. The small number of glottic treatment failures had a good chance of salvage by vertical partial laryngectomy if recurrence or a new primary was detected early. Recurrence of supraglottic cancer was salvaged occasionally by horizontal partial laryngectomy if strict indications were observed. Total laryngectomy remained the final minority salvage option.

KEY WORDS — irradiation, laryngeal cancer, partial laryngectomy.

The number of new cases of laryngeal cancer in the United Kingdom appears to have been relatively stable over the past 20 years, although there is slight evidence of a relative increase in women.[1,2] It is also well established in Britain that glottic primary lesions are more frequent than supraglottic lesions (32% supraglottic, including epilaryngeal sites, to 60% glottic).[3] In most of Northern Europe this pattern of regional frequency also holds good, but the exact reverse is apparent for people of Southern European origin and in Finland, who show a much greater relative incidence of supraglottic lesions (60% supraglottic to 30% glottic) and a higher total incidence of laryngeal cancer[2] (also Y. Cachin, personal communication, 1976).

PHILOSOPHY OF CARE

In the United Kingdom for the last 40 years laryngologists have enjoyed the facilities and support of skilled radiotherapists, often isolated but working in regional departments readily accessible to the larger population groups. These facts, with excellent figures for cure obtained by irradiation in the more common cases of limited glottic cancer,[3,4] coupled with the potent philosophy of "painless cure" and "saving the patient from surgical mutilation," have resulted in many years of radiotherapeutic domination in the treatment of laryngeal cancer. In recent years this attitude has been slowly changing with a realization of the greater effectiveness of combined treatment in advanced lesions and the more selective application of irradiation or surgery in early cases (T1 and T2), deriving mainly from experience in combined head and neck clinics.

The economic and geographic factors of "free at the time" treatment and "free" transportation provided by the National Health Service have also tilted the balance in favor of the more prolonged but less traumatic outpatient treatment by irradiation. As a result of this predominance of radiotherapy, United Kingdom hospital centers are in a unique position to assess the application of surgical techniques after failed full-dosage therapy.

MATERIAL STUDIED (LARYNGEAL CONSERVATION SURGERY)

To illustrate contemporary usage in the United Kingdom, two approximately parallel time periods have been chosen at two hospitals in London dealing frequently with laryngeal cancer. At The Royal Marsden Hospital the period 1963 to 1988 is taken, and at The Royal National Throat, Nose and Ear Hospital partial laryngectomy for the period 1961 to 1988 is reviewed. A total of 50 patients underwent forms of either vertical or horizontal partial laryngectomy at the former hospital. Only one malignant tumor out of the vertical group was treated initially by surgery. During the same period in the horizontal group 11 patients had initial supraglottic laryngectomies without prior irradiation, 5 of which were for benign lesions. Altogether, 15 patients underwent horizontal partial laryngectomy after irradiation. For the same period a total of 410 total laryngectomies were carried out (Table 1).

A total of 68 partial laryngectomies were performed at the latter hospital (1961 to 1988). Vertical partial laryngectomy accounted for 57 of these, in 12 patients being extended into a frontolateral operation. Surgery followed irradiation in 37 patients, and 16 were not irradiated, with 4 having ra-

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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TABLE 1. PARTIAL LARYNGECTOMIES AT THE ROYAL MARSDEN HOSPITAL, 1963 TO 1988

Type of Operation			*No.*
Vertical	After full irradiation		23
	Nonirradiated		1
	Total	24	
Horizontal	After full irradiation		15
	Nonirradiated (5 benign lesions)		11
	Total	26	
Total			50

Age range was 24 to 78 (median, 59). Male-to-female ratio was 39:11. There were 410 total laryngectomies in same period.

TABLE 2. PARTIAL LARYNGECTOMIES AT THE ROYAL NATIONAL THROAT, NOSE AND EAR HOSPITAL, 1961 TO 1988

Type of Operation			*No.*
Vertical	After full irradiation		37
	Irradiated postoperatively		4
	Nonirradiated		16
	Total	57	
Horizontal	After full irradiation		5
	Irradiated postoperatively		2
	Nonirradiated (3 benign lesions)		4
	Total	11	
Total			68

Age range was 43 to 85 (median, 62). Male-to-female ratio was 62:6. There were 650 total laryngectomies in same period.

diotherapy after surgery. Five of the 11 horizontal partial laryngectomies were performed after irradiation, and 6 patients were treated initially by surgery, 2 being irradiated after operation. In the same period 650 total laryngectomies were carried out (Table 2).

The above figures of 410 and 650 total laryngectomies are given only to emphasize the ratio of radical (1,060) to conservation (118) procedures carried out at the two hospitals in the period studied. All cases of laryngeal cancer at both hospitals judged to require total laryngectomy for cure are included (mainly T3 and T4; primary and secondary referrals). The component representing radical salvage surgery after failed irradiation in T1 and T2 tumors would comprise about 10% of the whole.

In laryngeal cancer recurrent after irradiation, clinical classification and suitability for a conservation procedure cannot be finally determined, at least until the direct laryngoscopy that should immediately precede any surgical intervention. In many doubtful cases it was also found on direct exploration of the larynx at operation that extensions of the tumor rendered partial resection unwise or impossible despite a favorable endoscopic assessment. This finding underlines the practical necessity to obtain prior permission for total laryngectomy in every case and to refrain from unqualified positive assurances to the patient regarding conservation before the event.

RADIOTHERAPY

Irradiation of patients from both hospitals was given in the Radiotherapy Department of The Royal Marsden Hospital. The radiation source has been almost entirely the 5,000-Ci telecobalt apparatus. In a few earlier cases, the older 12-g radium bomb was used. Total tumor dose per patient has averaged 65 Gy to the larynx, fractionated as once daily 5 days per week over a period of 6 to 7 weeks.[3]

The two lateral fields (5 x 4 cm) used for early glottic cancer were solely confined to the larynx itself. However, lateral fields for supraglottic cancer (10 x 8 cm) also included the upper neck lymphatics, tongue base, and thyrohyoid area, where irradiation was concentrated during the latter part of treatment. It is clear that the laryngeal vestibule and preepiglottic tissues probably received a maximal tumor dose that of necessity has influenced healing after surgical salvage.

TYPES OF OPERATION

At both hospitals the vertical operations were of a standard pattern using a midline vertical skin incision or a horizontal incision at the level of the lower third of the thyroid cartilage. After thyrotomy, the resection then extended from the anterior commissure posteriorly to include the whole vocal cord and intrinsic laryngeal musculature back to the arytenoid vocal process, and from the upper surface of the ventricular band to 5 mm below the edge of the true vocal cord. In all cases a major portion of the thyroid cartilage on the affected side was excised. In the period studied at the two hospitals, there were 16 extended vertical operations (hemilaryngectomies), 5 of which included the anterior commissure and the anterior third of the opposite vocal cord.

Most horizontal supraglottic operations were also standard, mainly following the technique of Som[5] using a T-shaped skin incision with the horizontal component at the hyoid level and the vertical component offset about 5 cm from the midline to the side mainly involved. Resection then included the epiglottis, valleculae, preepiglottic space and hyoid bone, ventricular bands, and ventricles with part of the aryepiglottic folds. However, in 7 of the 26 operations at The Royal Marsden Hospital, the resection was extended. Two operations included one arytenoid cartilage in each specimen, one of these also being extended to resect a vocal cord and adnexae on the same side, and one to include the top of the pyriform fossa on the same side. Five others were extended to resect part of the tongue base.

The majority of patients had had one previous full course of telecobalt irradiation to a total dose of approximately 65 Gy at various intervals prior to

TABLE 3. COMPLICATIONS FOLLOWING PARTIAL LARYNGECTOMY AFTER FULL IRRADIATION AT THE ROYAL MARSDEN HOSPITAL, 1963 TO 1988

Operation	*Time After Operation*	*No. of Pts*
Vertical (23 patients)		
Subcutaneous emphysema	< 10 days	4
Mild chest infection	< 14 days	4
Delayed swallow	< 6 weeks	2
Perichondritis with delayed decannulation	< 4 months	3
Persistent laryngeal edema with delayed decannulation	16 months	1
Intralaryngeal granuloma	6 months	1
Soft tissue wound infection	14 days	1
Late subglottic stenosis (surgical correction required)	7 years	1
No complications		15
Horizontal (15 patients)		
Delayed swallow	6 to 8 weeks	6
Delayed swallow (temporary gastrostomy)	1 year	1
Swallow solids only (gastrostomy and tracheotomy)	6 years	1
Bronchopneumonia	2 to 6 weeks	6*
Spontaneous small fistula	7 weeks (natural closure)	1
Established primary fistula	6 weeks (secondary closure)	1
Gross wound breakdown	10 weeks (secondary closure)	1
No complications		6

*Total laryngectomy obligatory in one patient.

operation. Of the 15 radical neck dissections carried out, all but 1 were for clinically positive nodes. One was simultaneous with a vertical partial laryngectomy and another was staged after the same procedure. The other 13 were for supraglottic lesions and were also staged in order to minimize healing and swallowing difficulties.

COMPLICATIONS

Ward[6] draws necessary attention to at least a dozen major complications of laryngeal conservation surgery that require careful management if they are to be avoided.

Of the 81 vertical operations carried out at the two hospitals, most complications occurred in the 60 cases operated on after full irradiation. (Table 3 shows those for The Royal Marsden Hospital.) Even so, they were usually temporary and seldom serious. Perichondritis causing delayed decannulation, subcutaneous emphysema, and mild chest infections in a few cases were the main problems. One patient developed an intralaryngeal granuloma 6 months after operation. In another, laryngeal edema following perichondritis lasted 16 months, and in a third, subglottic stenosis requiring surgical correction developed 7 years after operation.

The postoperative picture for the 37 horizontal partial laryngectomy cases gave more cause for concern, particularly in the 20 patients operated on after irradiation. (Table 3 shows the complications at The Royal Marsden Hospital.) Only 8 of these cases healed per primam with no complications, and none was an extended procedure.

At least half experienced delayed return of normal swallow, sometimes up to 8 weeks. One patient required gastrostomy for 1 year, and another for 6 years, at which time total laryngectomy became necessary for recurrence. A variable degree of bronchitis and bronchopneumonia up to 6 weeks postoperation was also common in many patients with delayed swallow. In one, total laryngectomy was necessary for relief.

Another serious problem following the horizontal operation after irradiation was wound breakdown and fistula formation. This occurred in four patients, three of whom had had extended procedures and then required secondary repair by regional flap.

Tracheal decannulation was usually possible within 7 days of operation after the vertical procedure and 14 to 21 days after the horizontal operation in patients with no complications. There were no postoperative deaths directly attributable to surgery.

FUNCTIONAL REHABILITATION

Healing is inevitably delayed in fully irradiated tissues to an unpredictable degree. It is felt that removal of three quarters of the ala of the thyroid cartilage in the vertical operation facilitates slow healing that is probably not complete for at least 6 weeks. In the horizontal operation, partial removal of the upper parts of the thyroid cartilage may also assist healing, and is essential for access and closure. Care must be taken in these maneuvers to avoid unnecessary damage to the external and recurrent laryngeal nerves or their main branches.[5,6]

The assistance of the speech therapist is of great benefit to a patient's morale after operation and to the eventual quality of speech regained. During the immediate healing period attempted use of the voice should be minimal, with an absolute ban on smoking, vocal stress, or alcohol.

Following the horizontal supraglottic operation the greatest problem relates to regaining the natural swallow and the prevention of chest infection by spillover. Much has been written on this subject and the problem is aggravated by the increased local edema and delayed healing in irradiated patients, and also by surgical trauma to the external laryngeal nerve. Experience so far would indicate that any extension of the standard supraglottic operation invites disaster in such patients — more especially since repair of the sphincter mechanism cannot be

TABLE 4. END RESULTS OF PARTIAL LARYNGECTOMY AFTER FULL IRRADIATION

Type of Operation	*No. of Pts*	*Local Recurrence*	*Cervical Metastases*	*Neck Dissection*	*Died of Other Causes*	*Died of Disease*	*Alive and Well >3 y*
The Royal Marsden Hospital, 1963 to 1985*							
Vertical	19	3	1	1	2	2	13 (68.4%)
Horizontal	13	2	7	7†	2	5	5 (38.4%)
The Royal National Throat, Nose and Ear Hospital, 1961 to 1985*							
Vertical	35	6	2	1	6	4	23 (65.7%)
Horizontal	4	1	4	3	1	2	1 (25.0%)
Totals							
Vertical	54	9	3	2	8	6	36§ (66.6%)
Horizontal	17	3	11	10†	3	7	6 (35.3%)

*Patients free of disease 1985 to 1988.

†Three were bilateral.

§Does not include seven patients salvaged by total laryngectomy.

carried out with any assurance in the irradiated larynx. Furthermore, even when swallowing has recovered, with increasing age there is a likely increase in morbidity and even mortality from recurrent spillover due to dyskinesia of the swallow reflexes. Stell[7] reported recurrent chest infection in half of his nonirradiated supraglottic laryngectomy patients. This conclusion is well supported radiologically by Murray,[8] who retrospectively assessed the high incidence of postoperative pulmonary complications in these same patients. Another report, by Ellis,[9] indicates that salvage by total laryngectomy was required for repeated aspiration and lower respiratory tract complications in two of three patients who had partial supraglottic operations for recurrence after irradiation.

The value of cricopharyngeal myotomy seems equivocal. In all it was carried out in only eight (30%) patients out of the total 26 supraglottic operations at The Royal Marsden Hospital. Four of these eight, having had extended operations, did not in fact rehabilitate well, and two subsequently required gastrostomy. However, it is a simple step that may assist swallowing and easily performed at the time.

After full-dosage irradiation it is felt that there is no place for the more sophisticated reconstructive procedures such as cartilage transposition, muscle transplants, or fat or fascia grafts.[10] Repairs in this series comprised only the use of local mucosal rotation flaps and simple approximations, except for the use of twin deltopectoral skin flaps to close the large anterior cervical defect in one case of total breakdown already mentioned, and the use of a single deltopectoral flap in other cases of partial breakdown.

OTHER MEASURES

No special attempt is made to spare the finer branches of the ipsilateral internal laryngeal nerve, as it is felt that they must inevitably be divided at some point during the resection. However, the external laryngeal and recurrent laryngeal nerves and their main branches should be preserved when possible.

Radical neck dissection was needed for clinically positive nodes on 13 occasions in 10 patients requiring horizontal partial laryngectomy, 3 patients having bilateral dissections. These were all staged in view of the increased risks to healing and swallow in those that are simultaneous. This was emphasized in 1 patient who developed quite severe dysphagia for a few weeks immediately after neck dissection although swallow had recovered well after the initial laryngeal resection.

Normal blood cytologic results and hemoglobin levels were mandatory and all patients were placed on wide-spectrum antibiotic cover for at least 3 weeks from the day before operation. Surgical technique was intentionally as atraumatic and meticulous as possible and omitted the use of coagulating diathermy. Any septic foci in the teeth or upper air passages were also eliminated before operation.

Finally, criteria for selection should include good cardiopulmonary function and general health. A chronologic upper age limit of about 65 is desirable[5] but 20% of patients in the quoted series were over that age. Blood loss at operation must be made good without delay by whole blood replacement, and strict attention must be given to postoperative drainage, dressings, and intensive care.

END RESULTS

The numbers of patients treated were insufficient to draw any absolute conclusions, but enough to indicate certain trends. There would seem little doubt that for the two hospitals combined, a minimum 3-year survival rate of 66.6% for patients undergoing vertical partial laryngectomy after failed irradiation is significant in spite of some healing delays and other minor complications. This figure does not include seven patients subsequently salvaged after further local recurrence for a minimum of 3 years by total laryngectomy (Table 4).

By contrast, a minimum 3-year survival of only 6 of 17 patients having horizontal operations, giving a survival rate of 35.3%, together with the serious complications resulting and the high rate of local and regional recurrence (7 patients also died with metastatic disease), would indicate great caution in proposing these operations after full-dosage irradiation (Table 4).

CONCLUSIONS

Given the availability of complete therapeutic facilities, the majority of limited glottic cancers with unimpaired cord mobility should initially be treated by full-dosage external irradiation. The small number of treatment failures will have a good chance of salvage by vertical partial laryngectomy if recurrence or a new primary lesion can be detected early.[11-17] Exceptions, better treated by initial conservation surgery, are likely to be in patients under the age of 40, heavy smokers (more than one pack daily), regular heavy drinkers, and those with diffuse keratosis or edematous chronic laryngitis for reasons given previously.

It is felt that contraindications to the vertical partial operation or its extensions as applied to recurrence after irradiation can be given as follows.

1. Immobility of the affected vocal cord.
2. Arytenoid cartilage or mucosa directly involved by tumor.
3. More than one third of the opposite vocal cord involved by tumor.
4. Evidence of transglottic or subglottic spread of disease.
5. Evidence of perichondritis or thyroid cartilage invasion.

In supraglottic cancer the principle of primary irradiation (up to 65 Gy) for the majority of localized T1 or T2 cases followed by partial or total laryngectomy for salvage also seems acceptable. Initial treatment by supraglottic laryngectomy with neck dissection should generally be chosen for cases with clinically positive nodal metastases, perhaps followed by irradiation to the neck as combined therapy.[18]

It must also be said that for experienced surgeons initial treatment by horizontal partial laryngectomy and its extensions in selected patients, with neck dissection on an elective basis, may give as good results for cure but with greater morbidity than using primary external irradiation.[9,11,14] A degree of flexibility in the choice and sequence of the two main treatment modalities will be rewarded with better results.[18,19]

There would appear to be no advantage in preoperative planned irradiation to a modified dosage of 20 to 40 Gy with the ensuing probability of increased postoperative morbidity.[11,12,17,18]

It is felt that salvage by horizontal partial laryngectomy for supraglottic cancer recurrent after irradiation will be contraindicated unless the following conditions are met.

1. The primary lesion is small and confined to the anterior laryngeal vestibule, free of the anterior commissure from the start of irradiation.
2. The lesion is histologically well differentiated.
3. The patient has good cardiopulmonary function, is under the nominal age of 65, and has good general health.
4. Exceptional circumstances are present, such as refusal of total laryngectomy in a borderline situation, or a similar situation in a professional voice user.

It is also desirable that these patients should have been closely followed throughout treatment by the surgeon and radiotherapist together.

In all other situations and when in doubt, the safest and best treatment for persistent supraglottic cancer after full-course radiotherapy is total laryngectomy.

ACKNOWLEDGMENTS — I thank Dr D. Golding-Wood of The Royal National Throat, Nose and Ear Hospital, London, and Dr P. Gluckman of The Royal Marsden Hospital, London, for their valued assistance; Professor Sir Donald Harrison for access to clinical material at The Royal National Throat, Nose and Ear Hospital; and Karen Golden for the secretarial work.

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Ann Otol Rhinol Laryngol 100:1991

RECURRENT LARYNGEAL NERVE SECTION FOR SPASTIC DYSPHONIA: 5- TO 14-YEAR PRELIMINARY RESULTS IN THE FIRST 300 PATIENTS

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This presentation compares the preoperative voice recordings and the latest follow-up voice recordings, made 5 to 14 years postoperatively, of the first 300 patients with various degrees of spastic dysphonia whom we treated with recurrent laryngeal nerve (RLN) sections from 1975 to 1982. Voice therapy was usually given afterward and in some patients, when necessary, "fine tuning" surgery was performed later. The 243 patients who could be located were asked to answer a questionnaire regarding their voice production and communication abilities, and to make a voice recording. The preoperative and long-term postoperative voice recordings were analyzed by means of perceptual voice evaluation and acoustic analysis of the voice spectra. Fifteen percent developed recurrence of mild to moderate spasticity 6 to 24 months after the RLN section. This was curable with laser vocal cord thinning via direct laryngoscopy. Eighty-two percent of patients had little or no voice spasticity 5 to 14 years after their RLN section. The experimental alternative of injecting botulin directly into the vocal cord to temporarily paralyze it is discussed.

KEY WORDS — recurrent laryngeal nerve section, spastic dysphonia.

INTRODUCTION

Spastic dysphonia (SD) is a rare but severely disabling voice dystonia. Like other poorly understood neurologic disorders such as hemifacial spasm, torticollis, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, and Alzheimer's disease, it was long thought to be a psychological or stress-induced disorder rather than an organic one. This belief was based on the observation that the patient's laugh and falsetto or singing voice were clear, the vocal cords looked clear and adducted normally (but only during falsetto), the tightness in the voice usually worsened with stress, and two thirds of patients with SD were women, who were considered to be subject to hysteria. As a result of correct observation but faulty analysis, it was called "hysterical spastic dysphonia"[1,2] for over 100 years and continued to be treated with voice therapy, psychotherapy, tranquilizers, muscle relaxants, etc, even though it was never cured with these techniques and medicines.

It is now generally accepted that this is a neuromuscular disorder. Since it is not caused by a mucosal lesion, the surface of the vocal cord looks normal. Because the vocal cord adductors are normally contracted very tightly during singing (falsetto phonation), a patient with hypertonicity (hyperadduction, spastic dysphonia) of the vocal cords would be expected to sing with a clear tone. The fact that normal voices and voices crippled with SD are variable and sound tight and angry with stress does not prove stress causes SD. We hope that no one still believes that women are the weaker sex or are more hysterical than men, that hysteria is due to vapors rising from the uterus (which is the reason hysteria and hysterectomy have the same root), or that SD is due to hysteria. (Incidentally, this reasoning would preclude any males from having hysteria or hysterical SD, yet they constitute one third of our SD series.)

Unfortunately, no one bothered to prove that SD was a psychological instead of an organic disorder before basing all pre-1975 treatment on this assumption. Nor did anyone prove that relaxing the person or the brain would reverse the assumed cause of SD. In fact, we have not found a reference prior to 1976[3] that admits, much less stresses, that voice therapy, psychotherapy, tranquilizers, muscle relaxants, antihistamines, biofeedback, allergy treatment, chiropractic, acupuncture, etc, do not cure SD. These therapies failed because they were trying indirectly to treat the vocal cord hyperadduction or incoordination by trying to affect the brain with relaxing exercises or relaxing medicines instead of treating the vocal cords directly by mechanical lateralization of one of them, eg, with recurrent laryngeal nerve (RLN) paralysis. In retrospect, it is easy to see why this happened.

Spastic dysphonia is rare. Many voice therapists, otolaryngologists, and neurologists do not have an opportunity to see enough patients with SD to be able to diagnose it reliably, much less to confirm that we currently have no effective means of reversing the abnormal brain activity that is causing the problem. (To make reliable diagnosis easier, and to demonstrate the long-term effects of RLN section, K. Izdebski and H. Dedo have collected several patients' preoperative and late postoperative voice re-

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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cordings on a tape cassette [BC Decker Publishing Co, Philadelphia, Pa].)

Prior to 1976, the voice therapists, otolaryngologists, psychiatrists, psychologists, and neurologists who did correctly diagnose and follow up a large series of patients with SD did not publish papers stating that the treatment methods of the last 100 years do not work. Of course, chemotherapists do not write papers emphasizing that they have not cured a single squamous cell carcinoma, and otolaryngologists do not give presentations and publish papers emphasizing that patients with fixed metastatic squamous cell carcinoma lymph nodes that are 4 to 6 cm in diameter have ruptured capsules and are virtually incurable. Careers and medical practices are not built by presenting and publishing papers about medical treatments that do not work.

Since RLN section for SD was first performed in 1975, we have been recording our patients' voices preoperatively and postoperatively, and later when possible, to evaluate results. Over the last 5 years we have tried to locate and record the voices of the first 300 SD patients who had RLN sections at the University of California at San Francisco (UCSF) between September 1975 and December 1981. We had the clinical impression that these voices stabilize by 2 to 3 years after operation, and this study would provide a large series of patients whose voices could be evaluated more than 5 years after RLN section for SD and compared to their preoperative voices.

MATERIALS AND METHODS

Krzysztof Izdebski, PhD, Tony Sahley, MA, Mara Behlau, PhD, Carol Friedenberg, MA, and Wilda Flower, MA, made most of the preoperative and postoperative voice recordings. A questionnaire and request for a new voice recording was sent to the last known address of all patients who had an RLN section for SD at UCSF between September 1975 and December 1981. Starting in 1986 Sahley and in 1988 Behlau located as many patients as possible by letter and by calling the patient's last known telephone number, the nearest relative listed on the hospital chart, the referring doctors, and voice therapists. Finally, a person-tracing service was used to find the last 31 patients who could be located. Of the 300 patients sought, 243 or 81% were found and recorded from 1986 to 1990. Thirty-five patients had died and 1 had had a laryngectomy for cancer before a 5-year-plus voice recording could be obtained. This left only 21 (7%) patients, out of 300, who could not be located 5 to 14 years after their operation. (Several of these, such as the ones who had died, had had one or more voice recordings made in the first 5 years postoperatively, which showed their results were comparable to the 243 recorded successfully more than 5 years after operation.) Most of the voice recordings were made from a microphone or telephone line in our audiology and speech division. A few were made by other voice therapists in the United States and abroad, or by the patients themselves at home.

To compare the reliability of microphone and telephone voice recordings, several normal subjects' voices and SD patients' voices were evaluated directly and recorded on cassette tapes both from the usual microphone and from a telephone microphone. The voices were compared with perceptual auditory (acoustic) and spectrographic analyses. It was confirmed that normal, spastic, and breathy voices could be evaluated reliably both when recorded with a microphone in a voice therapy room and when the signal was taken directly from a telephone line.

The preoperative and latest postoperative voice recordings were then recorded onto a master tape, and three trained listeners (voice therapists who have each personally seen more than 50 patients with SD treated with voice therapy, botulin injection into the vocal cord, and/or RLN section) evaluated the recordings with auditory perceptual analysis. Each of the recorded voice segments was evaluated for the presence of mild, moderate, or severe spasticity and marked breathiness. Spectrograms were made from each voice recording, and the preoperative and latest postoperative voices were compared. The patients' evaluations of their present voices were also tabulated.

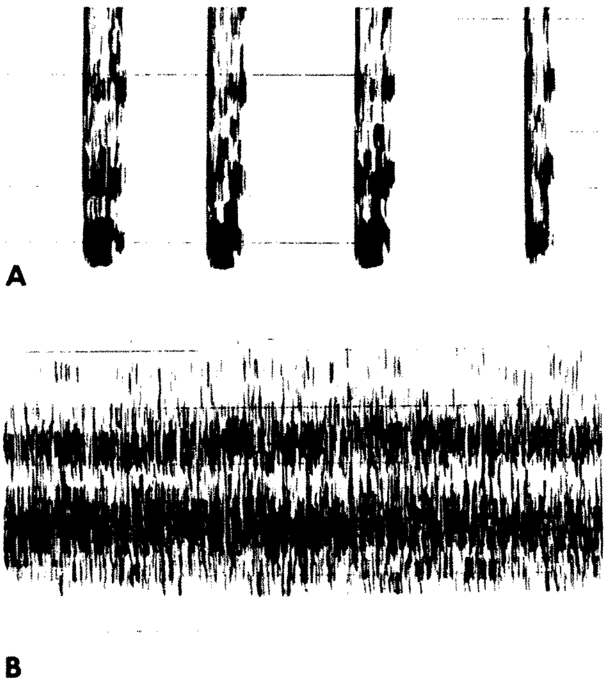
RESULTS

Of the 300 SD patients who had an RLN section at UCSF between September 1975 and December 1981, two thirds (207) were women and one third (93) were men. Their ages ranged from 21 to 92 years at the time of operation (see Table). Thirty-five patients (16%) had died and 1 required a laryngectomy before a 5-year-plus voice recording could be obtained. Twenty-one (7%) could not be located in spite of a major, expensive, multiyear effort. Thus, the voices of 243 (81%) patients were recorded 5 to 14 years after RLN section for SD.

Initial auditory perceptual analysis and comparison with preoperative voice spasticity by three trained listeners of these late postoperative voice recordings found no spasticity in 59% of patients, mild spasticity in 24%, moderate spasticity in 7%,

PATIENTS' AGES AT TIME OF RECURRENT LARYNGEAL NERVE SECTION

Decade	*No. of Patients*
20s	6
30s	35
40s	66
50s	87
60s	74
70s	25
80s	6
90s	1
Total	300



Spectrograms of vowel /a/ from one patient. A) Preoperative, showing long breaks and dark initial vertical striation. B) After recurrent laryngeal nerve section, showing noise between formants and little breathiness.

and severe spasticity in 10%. Thus, 83% had little or no voice spasticity even after such a long time. If recurrent spasticity developed it was most likely to have been in a patient with moderate or severe spasticity preoperatively, and it usually became apparent between 6 and 18 months postoperatively. Most patients with recurrent spasticity actually could eliminate it by talking at a slightly higher fundamental frequency than usual (ie, "up in the front of the mouth" or at the "hum" level), but they could not habitually use this spasticity-free voice, as voice therapists have observed for years in nonoperated patients. Self-assessment questionnaires were available from 216 patients (72%). Forty-five percent (98 patients) felt that spasticity was completely gone and 23% (51) felt it had recurred mildly (eg, was present when the patient was under stress or in a noisy place). Twenty-two percent (48 patients) felt that moderate spasticity had recurred and 8% (18) felt it was severe. (One patient did not respond.) Thus, by self-evaluation 68% had no spasticity or only a mild recurrence. When they compared their preoperative and present voices, 85% (184 patients) reported they were better, 7.9% (17) were the same, and 5.5% (12) felt they were worse. (Three patients had no response.)

Spectrographic analyses of recorded voice segments are still being evaluated, but some preliminary observations can be made. Spectrographic analysis tends to confirm the auditory perceptual analysis by trained listeners and it provides visual ("objective") proof of the elimination of spasticity by RLN section. Tremor (ie, semicyclic change in voice intensity and/or frequency) can be identified in about 34% of these 243 SD patients. The effect of RLN section on tremor is variable, but the presence of tremor in SD patients does not interfere with the ability of RLN section to eliminate spasticity (ie, it is not a contraindication). Voice stoppages ("breaks" or "squeezes"), or uncontrolled pauses of phonation from complete interruption of airflow, occurred in 52.8% of these 243 SD patients and had durations of up to 0.5 second. Voice stoppages were dramatically reduced or eliminated by RLN section and thus were not a contraindication to the procedure (see Figure). Both tremors and stoppages occurred preoperatively in 13.6% of the 243 patients. All voice stoppages were followed by a dark vertical striation showing the vocal folds were strongly adducted. Of course, in our patients who had RLN section we did not observe the so-called abductor type of SD perceptually or spectrographically. We call this "whisper dysphonia" and do not perform RLN sections for it because RLN blocks in a few of these patients did not help their voices.

Self-assessment of whether their voice had been improved by RLN section, available from 216 patients, gave a slightly better assessment than auditory perceptual analyses by trained listeners of voice recordings. Eighty-five percent (184 patients) felt their voices were better as a result of the operation; 7.9% (17) felt they were the same; 5.5% (12) felt they were worse; and 1% (3) did not answer.

Thus, 83% of the 243 patients whose voices could be recorded 5 to 14 years after RLN section have effective conversational voices. (Fifty-nine percent had no spasticity and 24% had occasional mild spasticity.) Seven percent had moderate and 10% had severe recurrence of spasticity. So far, 12% (28 patients) have had a laser vocal cord thinning via microdirect laryngoscopy that reduced or eliminated recurring spasticity. Several more are now planning to have this done.

DISCUSSION

Medical personnel often have been loath to discard ineffective treatments, from bleeding, cupping, and leeching to major head and neck operations for incurable cancers. This tendency was unfortunate when it wasted the patient's time and money, and worse when it caused complications and/or earlier death than no treatment. But it has been especially embarrassing when ineffective treatments have continued to be used for years after effective treatment was discovered. Examples of effective treatments that were slow to be adopted abound, including Semmelweis' hand-washing to prevent puerperal sepsis, Lempert's fenestration, Rosen's stapes mobilization, Shea's stapedectomy, and Alonzo, Som, and Ogura's supraglottic laryngectomy. Recurrent nerve section for SD may not be as important as the above examples, but it has been similarly spurned by some.

Medical personnel are correctly reluctant to adopt a new idea until it has been shown to be needed, low-risk, effective, and reliable. Regarding need, many otolaryngologists, voice therapists, neurologists, and psychiatrists, after correctly diagnosing a case of SD, still are unaware that it is not curable (ie, spasticity is not eliminated) with voice therapy, psychotherapy, muscle relaxants, tranquilizers, etc.[3-15] They still assume it is a psychoneurotic disorder in spite of a growing body of evidence that it is an organic neurologic disorder.[4-8,11] Eighty-four percent of the 77 SD patients in the 7-year Dallas Center for Vocal Motor Control study had abnormalities on brain imaging. Finitzo and Freeman concluded, "Spastic dysphonia is a supranuclear movement disorder primarily but not exclusively affecting the larynx."[6] Still, many medical doctors and voice therapists see no need to advise permanent vocal cord paralysis by RLN section or temporary vocal cord paralysis with repeated botulin injections into the vocal cord, even though these patients can be so disabled that they withdraw from society. Some have even lost their jobs and families, and several have considered or attempted suicide because of the disorder.

Recurrent laryngeal nerve section is obviously a relatively low-risk procedure. (Out of more than 400 operations, 2 brief incision infections occurred and there were no serious complications.) It is also effective. The spasticity initially has been eliminated, not only in our studies,[3,5,8,13,15] but in other series,[4,9,10,14] except for the five patients in whom one of the authors (H.H.D.) mistook a low branching of Galen's anastomosis (the pararecurrent nerve) for the main RLN trunk. When he reexplored these patients and sectioned the main RLN, they were no longer spastic after awakening from the anesthesia. These were "control operations" (albeit unplanned) and show that the procedure is not just psychogenically improving the voice because the patient expected it to do so, as some have suggested (J. H. Ogura, personal communication, 1978).

Aronson and DeSanto[4] have objected to RLN section on the grounds of reliability. They had a higher spasticity recurrence rate (64%) after 3 years than anyone else. Even Aronson and DeSanto's 34% success rate for elimination of spasticity after 3 years is much better than the occasional "partial or slight improvement" claimed by voice therapists,[6] psychologists, psychiatrists, etc. Our intermediate spasticity elimination rate of 85%[5] and now long-term success rate of 83% has been much better. DeSanto (personal communication, 1984) agreed that their results were different primarily because their selection criteria for the operation were different. They operated on the moderate and severe cases. Dedo and Izdebski[15] and others[14] have found that the recurrence rate is higher in this subgroup. Because the SD is bilateral,[13] the persistent dystonia in the mobile right vocal cord is stronger in these patients and after a few months it causes the mobile vocal cord to push further across the midline and overclose against the paralyzed left vocal cord. This cause of recurrence, rather than neural regeneration, is supported by the facts that 1) we place a silk ligature around the RLN stump, 2) visible mobility does not return to the paralyzed vocal cord when spasticity does recur, and 3) there is a lot of variation in the position assumed by the vocal cords and the compensation by the mobile cord in normal subjects and SD patients after RLN paralysis.[8] Furthermore, recurring spasticity can be corrected by laser thinning of the paralyzed vocal cord via direct laryngoscopy.[5,8,15] When the paralyzed vocal cord edge is moved to a wide enough paramedian position, or an intermediate position if necessary, the mobile vocal cord will not be able to adduct tightly against it, so again there will be a little breathiness and no spasticity, which is our goal. It can even be seen visually that when the edge of the paralyzed left vocal cord is far enough back from the midline to eliminate spasticity, there is a narrow (1 mm) visible glottic chink during phonation.

If there is a 2-mm chink, the voice will usually be breathy and weak enough that the reverse, a Teflon underinjection, may be considered. This has occurred in only about 15% of our patients and only 4% (12 patients) have insisted on a Teflon underinjection; the rest would not risk recurrence of spasticity. If the patient and surgeon refuse to accept some breathiness and reduced maximum volume (inability to be heard in loud noise, which, incidentally, was usually also the case before RLN section) and insist on moving the edge of the paralyzed vocal cord close enough to the midline to close the visible gap, spasticity will recur.

The other group objecting to RLN section admits that there is no effective medical (or psychological) treatment, but feels that section is undesirable because permanent. By injecting botulin directly into the vocal cord, they paralyze one or partially paralyze both vocal cords, "until a medical permanent cure is found."[11] (We believe we already have a permanent cure for the spasticity: RLN section with vocal cord thinning when necessary.) One of the authors (M.S.B.) has had experience with more than 50 SD patients injected with botulin. The patients do not like the fact that their spasticity is only partially or temporarily relieved. They have "roller coaster" voices and require reinjection every few weeks to months indefinitely, since it is unclear when, if ever, a "medical cure" will be invented. This procedure is still experimental; it requires injecting a poison whose long-term effects are unknown and there is now anecdotal evidence from single-fiber electromyographic recordings that botulin can affect neuromuscular junctions elsewhere in the body than the injection site. Repeated injections cause local atrophy, which can alter the contour of the vocal fold edge and permanently paralyze vocalis muscle fibers. This process can cause unpredictable effects on the quality of the voice. A theoretic concern is that SD patients already have an impairment of neuromuscular transmission and botulin may make them hypersensitive to the effects of other drugs that may further interfere with neuromuscular function such as certain antibiotics and anesthetics. The worst problem, though, is the psychological stress on the patient caused by repeated voice failure as the toxin's effects wear off and spasticity returns every few weeks to months.

This 5- to 14-year follow-up on our first 300 RLN sections confirmed the immediate result of elimination of spasticity and achievement of an effective conversational voice. Voice therapy is not effective preoperatively, but it does help to achieve the best possible voice if done correctly immediately postoperatively, so the voice is kept up in the front of the mouth at the "hum" level.

If spasticity recurs, it usually does so between 4 and 24 months after RLN section, as the paralyzed vocal cord contracts slightly toward the midline and the remaining mobile vocal cord adapts with stronger contractions (which is the reason for the volume increase during the first few months after RLN paralysis in nonspastic as well as SD patients). Even these patients usually have no spasticity when they phonate at the fundamental frequency of their hummed "m" up in the front of their mouth, but they are unable to learn this if they do not start soon after the RLN section. Significant spasticity has recurred in less than 20% of the 243 patients who could be located and whose voices were recorded (35 had died of unrelated causes, 1 had had a laryngectomy, and 21 could not be located). Laser vocal cord thinning has been effective in reducing or eliminating recurring spasticity by moving the edge of the paralyzed vocal cord laterally far enough so the mobile one cannot hyperadduct against it. If patients have too weak and breathy a voice 1 year or more after RLN section, when the voice has largely stabilized, a Teflon underinjection can reduce this breathiness. However, if enough Teflon is injected to move the vocal cord edge to the midline in an attempt to eliminate all breathiness and get normal volume, the spasticity will return. No paralyzed vocal cord recovered motion, although the arytenoid usually has the expected small adduction during phonation caused by contraction of the interarytenoid muscle (which still has partial innervation from the intact RLN) and the cricothyroid muscle (which has intact innervation from the superior laryngeal nerve).

CONCLUSION

We believe SD is an organic disorder of the central nervous system that is possibly due to viral injury or localized microvascular obstruction. It causes vocal cord dystonia or lack of fine muscle tension control similar to that of torticollis, facial spasm, and essential and intention tremor. All medical therapies for SD that are based on the assumption it is a psychoneurotic disorder that can be reversed have failed to cure it. It can only be diagnosed by listening with a trained ear, in which case it can usually be diagnosed over the telephone. The only effective treatment at the present time is paralysis of one vocal cord temporarily with botulin injection or permanently with left RLN section, which we do on the left side since it is the longer nerve and statistically more vulnerable to later spontaneous or traumatic paralysis. Thus, 83% of the 243 patients whose voices could be recorded 5 to 14 years after RLN section have effective conversational voices. (Fifty-nine percent had no spasticity and 24% had occasional or mild spasticity.)

These results are similar to those of Schiratzki and Fritzell,[14] who did a 12-year follow-up on 22 SD patients treated with RLN section. Eleven of the 22 had immediate good results, and the 25% in whom spasticity recurred had severe cases originally. The difference from Aronson and DeSanto's[4] 3-year follow-up of 33 patients, 64% (21 patients) of whom had "failed" voices, is probably due to case selection for surgery (L. W. DeSanto, personal communication, 1984), effectiveness of postoperative voice therapy (which failed to keep their voices at a high enough fundamental frequency to prevent spasticity), and the methods used to evaluate results.

Many patients would like to have a little more maximum volume so as to be heard better over loud noise. However, most of these patients had a similar problem in noisy environments preoperatively because of the spastic dysphonia, and oppose doing anything that would risk return of their SD. Therefore, only 4% (12 patients) have had a Teflon underinjection. Thirty-four percent of these operated SD patients also had essential voice tremor, diagnosed by its persistence during a falsetto "e," which, of course, eliminates SD but not tremor from the voice. The RLN section made it more apparent in some patients after the spasticity was eliminated and in others it was "loosened" and reduced in intensity. It needs to be recognized and brought to the patient's attention preoperatively so that he or she will be prepared for its persistence postoperatively, but it does not affect the result of RLN section for SD itself.

SUMMARY

The self-assessment questionnaire, auditory perceptual analysis, and acoustic spectrographic analysis confirmed that RLN section is immediately effective in eliminating spasticity (breaks, squeezes, tight strangled sounds) from SD patients' voices. Over 80% of these patients had little or no recurrence of spasticity after 5 to 14 years. Their voices usually

stabilized after 24 months, so future studies with 2- to 3-year follow-up should be valid.

ACKNOWLEDGMENTS — We thank Richard M. Flower, PhD, Robert G. Turner, PhD, Winifred Wong, and Sandy Wong for helping to provide and collect the data.

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VOCAL FOLD MEDIALIZATION BY SURGICAL AUGMENTATION VERSUS ARYTENOID ADDUCTION IN THE IN VIVO CANINE MODEL

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There are a variety of methods for treating unilateral vocal cord paralysis, but to date there have been few studies that compare these phonosurgical techniques by using objective measures of voice improvement. Vocal efficiency is an objective voice measure that is defined as the ratio of the acoustic power produced by the larynx to the subglottic air power. Vocal efficiency has been found to decrease with glottic disorders such as vocal cord paralysis and carcinoma. This study compared the effects of vocal fold medialization by surgical augmentation to those of arytenoid adduction on the vocal efficiency, videostroboscopy, and acoustics (jitter, shimmer, and signal-to-noise ratio) of a simulated unilateral vocal cord paralysis in an in vivo canine model. Arytenoid adduction was superior to surgical augmentation in vocal efficiency, traveling wave motion, and acoustics.

KEY WORDS — flaccid laryngeal paralysis, laryngoplasty, phonosurgery, recurrent laryngeal nerve, stroboscopy, vocal efficiency.

INTRODUCTION

There are a variety of methods for treating unilateral vocal cord paralysis. These include Teflon injection,[1] thyroplasty,[2] arytenoid adduction,[3] and nerve[4] and nerve-muscle pedicle transfer.[5] Most of these methods have been reported to improve the voice. However, recently, a theoretical paper comparing effects of the above treatment modalities on laryngeal vibration found significant differences among them.[6] Unfortunately, to date there have been few studies that compare these phonosurgical techniques by using objective measures of voice improvement. Most authors simply describe the voice as improved over the paralyzed state.

Vocal efficiency is an objective measure of the voice that was first studied by van den Berg[7] in 1956. He defined the efficiency of the voice as the ratio of the acoustic power of the voice to the subglottic power. The subglottic air power can be estimated as the product of the mean glottic airflow rate and the mean subglottic pressure. The physiologic control of vocal efficiency has been studied by several investigators. Koyama et al,[8] using an in vivo canine model, found higher levels of vocal efficiency when cricothyroid contraction was added to recurrent laryngeal nerve stimulation. Tanaka and Tanabe,[9] also using an in vivo canine model, found that increased contraction of the thyroarytenoid or cricothyroid muscle increased glottic resistance (the ratio of glottic airflow to subglottic pressure), while vocal efficiency remained constant. They further observed that contraction of the lateral cricoarytenoid muscle increased both glottic resistance and vocal efficiency. They postulated that thyroarytenoid muscle contraction plays a greater role in intensity control during normal phonation than lateral cricoarytenoid contraction by changing cord stiffness and shape, while lateral cricoarytenoid contraction plays a greater role in pathologic cases with incomplete glottic closure by enhancing cordal adduction. Clinically, vocal efficiency has been shown to decrease with some forms of laryngeal disease, such as invasive carcinoma and vocal cord paralysis.[10,11]

Although vocal efficiency is a useful objective measure of voice, it does have its shortcomings. This measure may not correspond with vocal quality. The voice may be quite harsh with a normal vocal efficiency. Also, vocal efficiency does not indicate the degree of control the patient has over the glottis. Typically, vocal efficiency increases with intensity, and an early vocal abuser may have a higher vocal efficiency despite actively abusing his or her voice.[9]

A number of acoustic measures of voice quality have been used clinically. These include jitter, shimmer, and signal-to-noise ratio. Jitter is defined as the fluctuation in the time interval between successive peaks of the fundamental frequency. Shimmer is the cycle-to-cycle variation in the amplitudes of the peaks. Signal-to-noise ratio is the ratio of the sound energy in the acoustic signal to the noise in the voice signal.[12,13] Lieberman[14] was the first to report an increased jitter in pathologic phonation. Lieberman[14] and Koike et al[15] found, using high-speed cinematography, that pitch perturbations reflected variations in the glottic area and periodicity. Koike et al[15] and Zyski et al[16] found increased jitter

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

REPRINTS — Gerald S. Berke, MD, Division of Head and Neck Surgery, UCLA, 10833 Le Conte Ave, Los Angeles, CA 90024.

and shimmer in patients with laryngeal tumors and unilateral vocal cord paralysis. Efforts have been made to use these measures as screening devices for laryngeal disease,[17] but few studies have used these measures to document the results of laryngeal surgery.[18]

An examination of current literature demonstrates that the optimal procedure for voice improvement in a patient with unilateral vocal cord paralysis is in a state of flux.[19] Teflon injection has been very successful in improving the voice and reducing aspiration since its introduction in 1962 by Arnold.[1] Rubin[20] studied the histology of Teflon-injected vocal cords and showed, using high-speed cinematography, improved vibration of the paralyzed cord, which was placed in a more medial position after injection. Von Leden et al[21] found voice improvement, postinjection, using both acoustic analysis and laryngeal function studies. Rontal et al[22] also demonstrated improvement in voice spectrograms postinjection. However, a number of concerns regarding Teflon injection are emerging.

The degree of improvement with Teflon injection is sensitive to the amount and position of injection.[23] Trapp et al[24] found, in the dog, that overinjection or underinjection of Teflon into the paralyzed cord would result in a lack of two-mass (upper and lower margin) vibration. Crumley et al[4] found, in humans, that Teflon-injected vocal cords lacked a mucosal wave. They postulated that the early voice fatigue often seen after Teflon injection may be due to sound's being generated by only the noninjected cord. Failure to achieve an improved voice has been reported to occur in about 10% of cases.[25] Acoustic studies by Trapp et al[24] using the in vivo canine model have shown that phonation after Teflon injection requires a high flow rate and has a high jitter. Cormier et al[26] measured forced inspiratory and expiratory airflow before and after injections and found a transient subclinical inspiratory airway obstruction at 24 hours after injection in all seven of the patients studied. This airway obstruction was thought to be due to postinjection inflammation of the paralyzed cord, which resolved in approximately 10 days. Rubin[20] demonstrated this inflammatory reaction histologically and warned that the voice may be worse up to 5 days after injection until the reaction subsides. He also showed that injection close to the free margin of the cord could increase its stiffness and interfere with its vibratory characteristics. Other complications of this procedure include granuloma formation, migration of Teflon, imprecise placement of Teflon, and overinjection with possible airway obstruction. The long-term effects of Teflon injection on the cord and the voice have not been reported. As an alternative to Teflon injection, a number of surgeons have begun to treat paralysis by laryngeal framework surgery.

Surgery on the laryngeal framework as a treatment for unilateral vocal cord paralysis began with Payer[27] and was later modified by Meurman[28] and others. The first systematic study and classification of these procedures was by Isshiki et al,[2] who coined the term thyroplasty. There are four types of thyroplastic operations. Type I provides lateral compression to the paralyzed cord, narrowing the glottic chink. Type II creates lateral expansion of the glottis. Type III shortens and relaxes the cord bilaterally. Type IV lengthens and stretches the cords. Isshiki et al[29] studied the results of these four types of thyroplasties in treating unilateral vocal cord paralysis in the canine larynx. In their study, the degree of voice improvement was evaluated subjectively as "improved" or "rough," and the mechanical effect on the larynx was studied only with laryngoscopy. They recommended using a type I thyroplasty for a unilateral recurrent laryngeal nerve paralysis and types I and IV together for a unilateral superior and recurrent laryngeal nerve paralysis. Clinically, there are four types of manual compression tests that can be performed on the larynx to help decide if thyroplasty would be helpful. These are the lateral compression test, the dorsal compression test, the cricothyroid approximation test, and combinations of the above.[30] Improvement in the voice during the lateral compression test helps indicate the degree of improvement after type I thyroplasty.

Koufman[31] reported a series of 11 patients who underwent a modification of the type I thyroplasty (medialization laryngoplasty) for treatment of unilateral vocal cord paralysis (both recurrent and vagal). On a five-point scale, improvement was seen in 10 of 11 patients. Escajadillo[32] reported a modification of the type I thyroplasty performed in dogs and humans. This modification resulted in a "near normal" or "normal" voice in 4 of 5 patients. Koufman found several advantages of medialization laryngoplasty over Teflon injection. The medialization is theoretically easily reversible, whereas Teflon injection is more difficult to reverse. The patient's discomfort is less with this procedure under local anesthesia than with a direct laryngoscopy under topical and local anesthesia. The surgeon can add to and subtract from the degree of medialization to fine-tune the voice, whereas the Teflon injection can only add to the medialization.

After their initial experience with the type I thyroplasty, Isshiki et al[3] noticed that unilateral laryngeal paralysis patients with a large posterior glottic chink or a difference in the level of the cords were not achieving optimal results. If the posterior glottic chink was large, it continued to leak air after type I thyroplasty. In five patients (two of whom had failed a type I thyroplasty), Isshiki performed an arytenoid adduction in which a suture was placed around the muscular process of the arytenoid and through the anterior thyroid cartilage, and tied it with

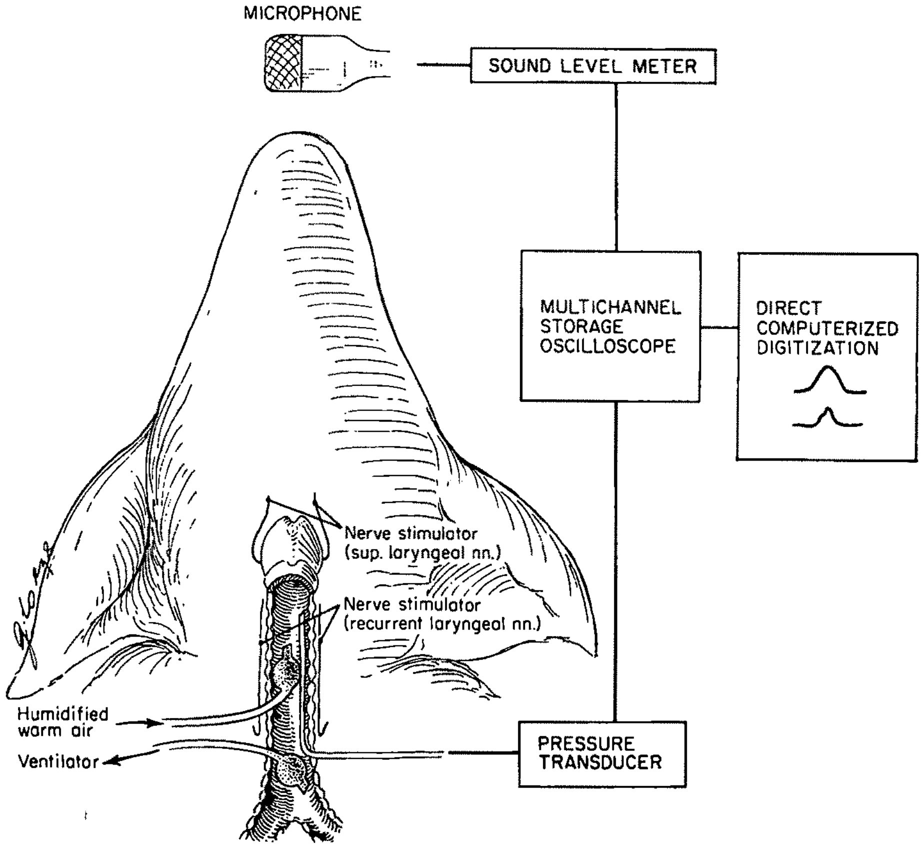
MICROPHONE
SOUND LEVEL METER
MULTICHANNEL STORAGE OSCILLOSCOPE
DIRECT COMPUTERIZED DIGITIZATION
Nerve stimulator (sup. laryngeal nn.)
Nerve stimulator (recurrent laryngeal nn.)
Humidified warm air
Ventilator
PRESSURE TRANSDUCER

Fig 1. Schematic representation of experimental setup for in vivo canine model of phonation.

enough tension to adduct the arytenoid to the midline. This was performed as an open neck dissection under local anesthesia. Postoperatively, all five patients had improved spectrograms.

The first reported arytenoid procedure for vocal cord adduction was by Morrison,[33] who used an open procedure to release the posterior cricoarytenoid muscle from the muscular process, and sutured the arytenoid in the midline after removing a piece of cricoid to adjust the level of the cord. Montgomery[34] used a laryngofissure to gain access to the glottis and then pinned the arytenoid to the cricoid in the midline position.

This study used an in vivo canine model to compare vocal fold medialization by surgical augmentation to arytenoid adduction in improving the vocal efficiency, videostroboscopy, and acoustic properties (jitter, shimmer, and signal-to-noise ratio) of a unilateral vocal cord paralysis.

MATERIALS AND METHOD

In Vivo Canine Model. Mongrel dogs (25 kg) were premedicated with Innovar intramuscularly. Intravenous Pentothal was administered to a level of corneal anesthesia and additional Pentothal was used to maintain this level of anesthesia throughout the experiment.

The animal was placed supine on the operating table, and a midline incision was made to expose the trachea from the hyoid to the sternal notch. Both recurrent laryngeal nerves were identified and preserved. Both superior laryngeal nerves were identified along their course to the cricothyroid muscles. A low tracheotomy was performed at the level of the suprasternal notch, through which an endotracheal tube was passed to allow ventilator-assisted respirations. A second tracheotomy was performed in a more superior location, through which a cuffed endotracheal tube was passed in a rostral direction and positioned with the tip 10 cm below the vocal folds. The cuff was inflated to just seal the trachea. Humidified heated air was passed through this rostral endotracheal tube from a compressed air tank. Flow was controlled with a valve and measured with a Gilmont flowmeter. The air was humidified and heated by being bubbled through 5 cm of heated water so that the temperature of the air was 37°C when measured at the glottic outlet. A 1-cm four-holed plastic shirt was used to suspend the epiglottis from a fixed point to provide direct visualization of the larynx through the oral cavity (Fig 1).

One-centimeter segments of recurrent and superior laryngeal nerves were isolated, and Harvard miniature electrodes were applied around each nerve. The electrodes were then insulated from surrounding tissue. Two constant-current nerve stimulators (model S2LH, WR Medical Electronics, St Paul, Minn) were used to stimulate the recurrent and superior laryngeal nerves independently. These nerves were stimulated at 70- to 80-Hz stimulus frequency with 0.5- to 2.0-mA intensity for 1.5 milliseconds. Phonation was produced with an airflow of 318 to 523 mL/s applied through the larynx by the rostral endotracheal tube.

Surgical Technique. Arytenoid adduction was performed as described by Isshiki et al.[3] The thyroid cartilage was exposed down to the posterior margin. The constrictor muscles were elevated and sectioned off. Dissection proceeded on the inner surface of the thyroid cartilage. The mucosa of the pyriform recess was elevated to identify the muscular process of the arytenoid. One 4-0 braided nylon suture was placed around the muscular process of the arytenoid and then out through the thyroid ala by using a Keith needle. The tension on the stitch was adjusted with a clamp to allow maximum acoustic intensity for a given airflow rate and subglottic pressure.

The surgical augmentation used for vocal cord medialization followed the method of Hiroto.[35] This method was chosen because of the more caudal position of the vocal fold with respect to the thyroid cartilage in the dog as compared to the human. The external perichondrium of the medial lower margin of the thyroid cartilage was incised at the junction between the cricothyroid membrane and the thyroid cartilage, on the side of the paralyzed vocal fold. A tunnel was created, by using a Freer dissector, through the inner perichondrium. A rectangular piece of polystyrene plastic (Styrofoam) tapered at the anterior and posterior edge, 2 to 4 mm in thickness, was then placed in this tunnel to medialize the paralyzed cord. This piece of Styrofoam was reshaped as necessary to achieve optimal volume for a given airflow rate and subglottic pressure.

Acoustic Measures. Acoustic measures were made with a 1-in Bruel & Kjaer condenser microphone placed 30 cm from and level with the glottic outlet. The microphone was directed 90° from the direction of the sound source. The sound level measurements were made in decibels with a Bruel & Kjaer sound level meter type 2209 on the C-scale. The acoustic signal was also digitized, after C-scale filtering, at 20 kHz and stored on the hard disk of a personal computer.

Subglottic pressure was measured with a Millar Mikro-Tip catheter pressure transducer (model SPC-330, size 3F) passed rostrally through the superior tracheotomy. It was placed 5 cm below the glottis. This signal was low-pass-filtered at 3 kHz, digitized at 20 kHz, and stored in a personal computer. Owing to the variation in subglottic pressure during phonation, the peak pressures attained during the glottic cycle were used. These peaks were identified by using a commercially available software package for the personal computer system (C-Speech, Paul Milenkovic, University of Wisconsin, Madison, Wis). The pressure transducer was calibrated before each experiment against a mercury manometer.

Vocal efficiency was calculated as the ratio of the acoustic power of the voice to the subglottic power. The total acoustic power was calculated by the method of Koyama et al,[8] in which total sound power = $2r^2Pe^2/Poc$. This formula applies for a sound power radiating with no known directivity into a hemisphere of area $2r^2$, a distance "r" away from the source. The product of Po (the density of the medium) and c (the velocity of propagation) is the specific acoustic impedance of the medium, which is 41.1 dynes x s/cm^3 in air at 20°C. The term Pe is the root mean square sound pressure in dynes per cubic centimeter at the distance "r" from the sound source. The subglottic power was calculated as the product of the flow rate times the peak subglottic pressure.

Acoustic analysis of the digitized acoustic signal was performed with a commercial software program (C-Speech). Jitter, shimmer, and signal-to-noise ratio were calculated for each trial.[10] The background noise in the laryngeal laboratory was 35 dB lower than the experimental values, in using the C-scale. To normalize for varying fundamental frequency, jitter was calculated as a fraction of the period of the fundamental frequency.

Videostroboscopy. For stroboscopic imaging of the larynx, a Storz laryngostrobe unit (model 8000) was used. The stroboscope was connected to a Storz 0° telescope via a fluid-filled light cable. The image was detected by a Jedmed CCD (charge-coupled device) video camera (model 70-5110) and a Sony U-matic videocassette recorder (VO-5850). The video images were analyzed frame by frame with the videorecording unit.

Experimental Design. Eight adult mongrel dogs were used for this study. Measurements for vocal efficiency and acoustic analysis (jitter, shimmer, and signal-to-noise ratio) were obtained on a minimum of two to four trials, followed by videostroboscopy, for each experimental state: normal (simultaneous bilateral recurrent laryngeal nerve and superior laryngeal nerve stimulation), unilateral recurrent laryngeal paralysis, paralysis plus arytenoid adduction, paralysis plus surgical augmentation, and paralysis plus adduction and augmentation together. A mean value for vocal efficiency, jitter, shimmer, and signal-to-noise ratio was then computed from the trials for each experimental state. The order of the surgical manipulations was changed for each dog to reduce any ordering effects. Stimulation of the recurrent and superior laryngeal nerves in the normal state was optimized to create the greatest intensity, because vocal efficiency has been found to increase with intensity.[10]

Statistical Analysis. Each experimental state (normal, unilateral recurrent laryngeal nerve paralysis,

TABLE 1. VOCAL EFFICIENCY

Dog	*Normal*	*Paralysis*	*Arytenoid Adduction*	*Augmentation*	*Adduction and Augmentation*
1	3.0	0.098	2.4	0.69	4.6
2	14	1.5	18	1.3	8.9
3	2.8	0.055	2.5	0.095	2.4
4	23	0.065	9.8	0.065	11
5	11	0.2	11	0.68	45
6	43	1.4	2.1	3.9	3.3
7	70	0.065	14	0.35	4.9
8	49	1.3	57	1	63
Mean	27	0.58	15	1	18

All values are times 10^{-4}.

paralysis plus arytenoid adduction, paralysis plus augmentation, and paralysis plus adduction and augmentation together) was compared for statistical significance by using a one-way analysis of variance for repeated measures for the dependent variables vocal efficiency, jitter, shimmer, and signal-to-noise ratio.

RESULTS

Vocal Efficiency. Table 1 lists for each dog the vocal efficiency for each experimental state. For the normal canine larynx the vocal efficiency varied from 3 x 10^{-4} to 1 x 10^{-3} with a mean of 2.7 x 10^{-3}. For recurrent laryngeal nerve paralysis the vocal efficiency decreased in every case by at least a factor of 10. The values for paralysis varied from 5.5 x 10^{-6} to 1.3 x 10^{-4} with a mean of 5.8 x 10^{-5}. Even the least efficient normal larynx was more efficient than the most efficient larynx with recurrent laryngeal nerve paralysis.

The efficiency of the paralyzed larynx after arytenoid adduction varied from 2.1 x 10^{-4} to 1.8 x 10^{-3} with a mean of 1.5 x 10^{-3}. In every case, the arytenoid adduction improved the vocal efficiency of the paralyzed larynx. The degree of improvement varied by a factor of 1.5 to 150.

The efficiency of the paralyzed larynx after surgical augmentation varied from 6.53 x 10^{-6} to 3.9 x 10^{-4} with a mean of 1.0 x 10^{-4}. In all cases but two, there was an improvement in the efficiency over the paralyzed state. The degree of improvement varied by a factor of 0.3 to 23.

When both arytenoid adduction and surgical augmentation were used together on the paralyzed larynx, the vocal efficiency varied from 2.4 x 10^{-4} to 4.5 x 10^{-3}, with a mean of 1.8 x 10^{-3}. The degree of improvement over the paralyzed larynx varied by a factor of 2.4 to 222. In every case, arytenoid adduction and augmentation together improved the efficiency of the paralyzed larynx.

The vocal efficiency scores for arytenoid adduction and arytenoid adduction and augmentation to-

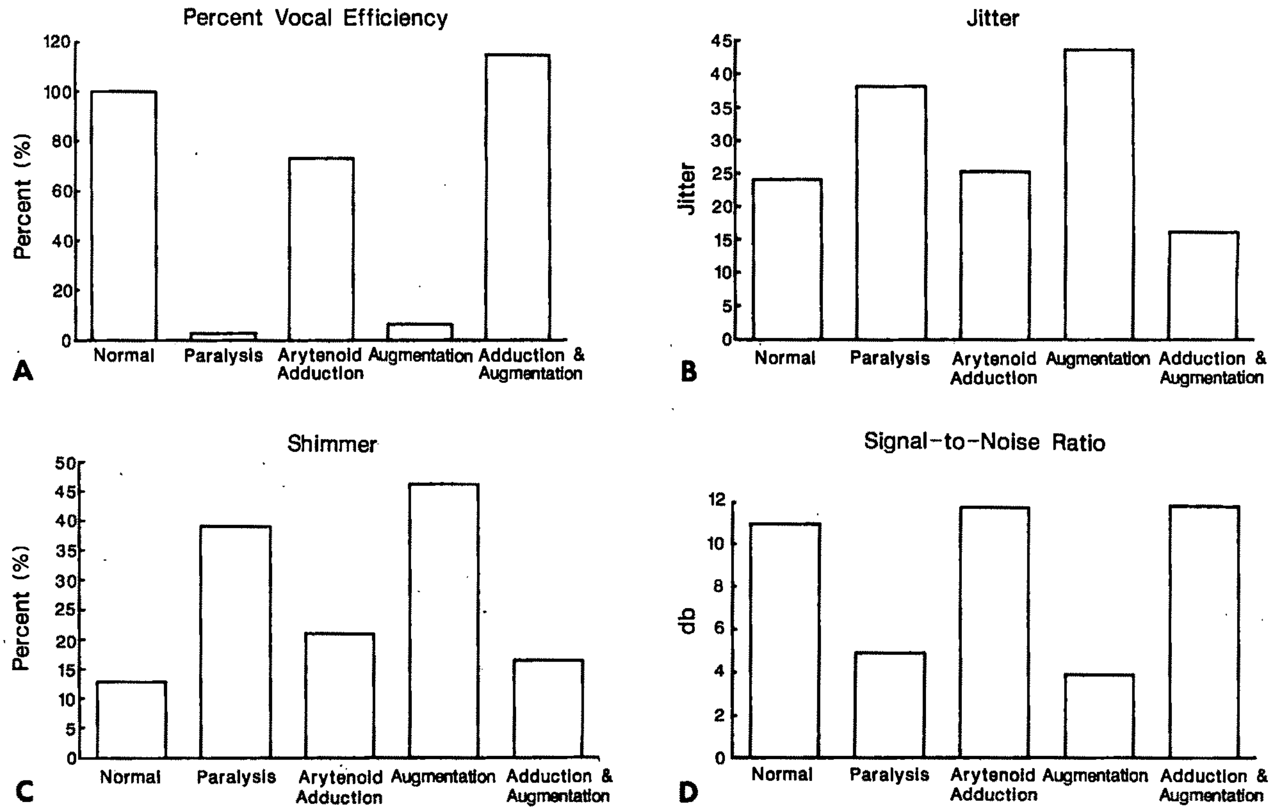

Fig 2. Results. A) Percent vocal efficiency for each experimental state. B) Jitter for each experimental state. Jitter is normalized over period (jitter ms/period ms) and expressed as times 10^{-1}. C) Shimmer for each experimental state. D) Signal-to-noise ratio for each experimental state, expressed as dB = 20log10(signal intensity/background intensity).

TABLE 2. SUMMARY OF STROBOSCOPIC ANALYSIS

Laryngeal State	*Glottic Closure*	*Mucosal Motion*	*Cord Motion*
Normal	Complete	Two-mass bilaterally	Sym
Paralysis	Incomplete; PGL	One-mass on paralyzed cord	Asym
Arytenoid adduction	Complete	Two-mass bilaterally	Asym
Augmentation	Incomplete; PGL	One-mass on paralyzed cord	Sym
Adduction and augmentation	Complete	Two-mass bilaterally; Asym movement of upper margin	Sym

PGL — posterior glottic leak, Sym — symmetric, Asym — asymmetric.

gether were significantly different from those for recurrent laryngeal nerve paralysis. Augmentation was not found to be significantly different from the paralysis state. Arytenoid adduction was not found to be significantly different from adduction and augmentation together ($F_{4,28} = 4.51$; $p < .01$).

In order to aid in comparisons between dogs, the efficiency of the normal larynx for each dog was expressed as 100% efficient, and the efficiency of the other states of the larynx was expressed as a percentage of normal. These results are shown in Fig 2A. The mean percent efficiency, across all dogs, was 3.0% for unilateral recurrent laryngeal nerve paralysis, 73% for arytenoid adduction, 7% for augmentation, and 115% for arytenoid adduction and augmentation together.

Acoustic Analysis. Figure 2B-D illustrates the jitter, shimmer, and signal-to-noise ratio, respectively, for each experimental state. The mean jitter values for unilateral recurrent laryngeal nerve paralysis and surgical augmentation were similar at 38 and 43, respectively. Jitter values for the normal larynges, arytenoid adduction, and arytenoid adduction and augmentation together were significantly lower ($F_{4,28} = 2.63$; $p = .05$) at 24, 25, and 17, respectively.

The mean shimmer values for unilateral recurrent laryngeal nerve paralysis and surgical augmentation were also similar at 39 and 47, respectively. Shimmer values for the normal larynges, arytenoid adduction, and arytenoid adduction and augmentation together were also significantly lower ($F_{4,28} = 4.17$, $p < .01$) at 13, 21, and 16, respectively.

The signal-to-noise ratios for unilateral recurrent laryngeal nerve paralysis and augmentation were similar at 5 and 4, respectively. Signal-to-noise values for the normal group, arytenoid adduction, and arytenoid adduction and augmentation together were significantly higher ($F_{4,28} = 5.88$; $p < .001$) at 11, 12, and 12, respectively.

In general, a unilateral recurrent laryngeal nerve paralysis resulted in a weaker acoustic signal (signal-to-noise ratio) with an increase in frequency and amplitude perturbation (jitter and shimmer). Arytenoid adduction or arytenoid adduction and augmentation together corrected these measures to a greater degree than surgical augmentation alone.

Stroboscopic Analysis. The stroboscopic data are summarized in Table 2. Phonation in the normal larynx revealed complete glottic closure and two-mass (upper and lower margin) motion of the mucosa on both cords, with complete symmetry. Unilateral recurrent laryngeal nerve paralysis revealed a mild posterior glottic chink incompetence and one-mass motion of the paralyzed cord. In addition, the paralyzed cord made greater lateral excursions than the normal cord, which remained more in the midline.

Surgical augmentation resulted in continued glottic incompetence at the posterior chink. The mucosa of the paralyzed cord had one-mass motion, while the normal cord had two-mass motion. The excursions of the two cords from midline were symmetric (as opposed to the paralyzed state).

Arytenoid adduction resulted in complete glottic closure and two-mass motion of the vocal fold mucosa bilaterally. The paralyzed cord demonstrated a greater lateral excursion from the midline, similar to that in the paralyzed state.

Arytenoid adduction and augmentation together resulted in complete glottic closure, with two-mass motion in the vocal fold mucosa bilaterally, but the upper margin of the paralyzed cord had a wider excursion of oscillation, crossing the midline after contact with the opposite cord. The motion of the bulk of the cords was symmetric, however.

DISCUSSION

In addition to the sound produced by the larynx, vocal efficiency is affected by the vocal tract and mouth radiation. In this study these last two factors were held constant so that glottic efficiency was measured. Koyama et al[8] found in dogs the normal range for vocal efficiency to be 0.06×10^{-4} to 2.0×10^{-3}, which agrees with our values of 3×10^{-4} to 1×10^{-3} with a mean of 2.7×10^{-3}. This value for canine vocal efficiency also approximates the range for humans of 0.45×10^{-5} to 45×10^{-5} found by van den Berg,[7] 0.3×10^{-4} to 14.0×10^{-4} by Isshiki,[36] and 0.11×10^{-4} to 6.8×10^{-4} by Iwata.[10]

In this study we examined vocal fold medialization by surgical augmentation and arytenoid adduction in treating unilateral recurrent laryngeal nerve paralysis in the dog. Vocal efficiency improved from approximately 3% of normal in the paralyzed state to only 7% after augmentation. The jitter, shimmer, and signal-to-noise ratio of surgical augmentation were also comparable to those of the paralyzed state.

Examination of the videostroboscopic images demonstrated that some of the failures of augmentation to improve vocal efficiency were from a leak of air in the region of a posterior glottic chink. This leak of air was a source of lost subglottic air power that was not converted to acoustic power. Titze,[37] using the excised canine larynx, found vocal efficiency to decrease with increasing glottal width. From both canine and human anatomic studies it has been shown that a type I thyroplasty cannot medialize the vocal process of the arytenoid, owing to the overlap of the cricoid cartilage under the posterior thyroid ala. Any attempt at medializing the vocal process using the thyroid lamina would just push against the posterior cricoid.[38]

The noise of turbulent flow from this posterior glottic leak may have contributed to the low signal-to-noise ratio of the surgical augmentation. Isshiki et al[39] found, using a life-size silicone model of the larynx, that turbulent noise was produced at the glottic chink when the speed of airflow through the chink exceeded a certain value (the critical Reynolds number). The intensity of the noise in Isshiki's model was proportional to the area of the glottic chink. The turbulent noise produced was distributed over a wide frequency range as in white noise.

There are some limitations in using the acute canine model of laryngeal paralysis. The posterior glottic chink between the vocal processes is longer in the dog than in the human. This difference may limit the performance of a surgical augmentation procedure in the dog. The problem of a leak in the posterior glottic chink may not be as significant a factor in the human. Using an acute model of laryngeal paralysis does not allow for atrophy of the paralyzed cord or compensation by the normal cord with time. These are interesting problems that deserve further investigation.

In this study, arytenoid adduction resulted in an average vocal efficiency that was 73% of normal (compared with 3% in the paralyzed state and 7% after surgical augmentation). The jitter and shimmer after arytenoid adduction were similar to those of the normal larynx and lower than those for the paralyzed state or after surgical augmentation. The signal-to-noise ratio for arytenoid adduction was also similar to normal and higher than for the paralyzed state or surgical augmentation. The values for arytenoid adduction and augmentation together seemed to follow those of arytenoid adduction alone.

It is difficult to speculate if the advantage of the arytenoid adduction was due to the dog's large posterior glottic chink. Although this study indicates that arytenoid adduction may be superior, in terms of vocal efficiency and acoustic analysis, to augmentation, careful preoperative and postoperative evaluation in humans is necessary.

The stroboscopic vibratory patterns of the vocal cords continued to demonstrate abnormalities after all treatment modalities. The larynges with arytenoid adduction, despite having two-mass motion of both mucosal folds, continued to have wide lateral excursions of the paralyzed cord. The augmentation failed to yield two-mass motion of the paralyzed cord, in addition to leaving a posterior chink leak. Even using arytenoid adduction and augmentation together resulted in an upper margin of the paralyzed cord that vibrated in wide excursions, crossing the midline after meeting the opposite cord. The reason these procedures failed to result in normal vocal cord vibration may be the lack of intrinsic vocalis muscle tone and stiffness provided by innervation. This intrinsic stiffness may be preserved by using reinnervation procedures.

Crumley et al[4] have recommended nerve transfer from the ansa hypoglossi to the recurrent laryngeal nerve as a treatment for unilateral vocal cord paralysis. This procedure was performed on five patients and the voice was thought to be superior to that produced by Teflon injection, owing to the restoration of normal stiffness, mass, and symmetry of the cord. Results on spectral analysis were improved postoperatively,[40] and stroboscopic examination revealed synchronous mucosal waves. This technique required an open procedure but did not expose or manipulate the larynx. Tucker and Rusnov[5] have also described a technique for laryngeal reinnervation using an ansa hypoglossi neuromuscular pedicle passed through a window in the thyroid cartilage.

How the reinnervation procedures would compare to surgical augmentation or arytenoid adduction in terms of vocal efficiency or acoustic analysis is presently under investigation.

Vocal fold medialization by surgical augmentation or arytenoid adduction, in this study, improved the vocal efficiency of the paralyzed larynx, but to different degrees. Under conventional reporting standards both results would be described as "good" or "improved." It was only through more objective measures, such as vocal efficiency and acoustic analysis, that any quantitative difference could be found. In this canine model, the vocal efficiency and acoustic properties of arytenoid adduction were superior to those of augmentation. As the number of treatments for unilateral vocal cord paralysis increases, it becomes important to document the results of each treatment by using objective measures. Practical approaches for achieving this goal have been reported, and it is our hope that the use of these methods will continue.[41-46]

CONCLUSIONS

Vocal fold medialization by surgical augmentation was compared to arytenoid adduction as a treatment for unilateral vocal cord paralysis. In this canine model, the vocal efficiency and acoustic properties of arytenoid adduction were superior to those of surgical augmentation.

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Ann Otol Rhinol Laryngol 100:1991

CELLULAR CHANGES IN REISSNER'S MEMBRANE IN ENDOLYMPHATIC HYDROPS

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A quantitative morphologic study of the cellular changes in human Reissner's membrane (RM) was performed under light microscopy on 30 normal temporal bones from 15 subjects, and on 20 temporal bones from 10 subjects with endolymphatic hydrops. The cellular density of the epithelial and mesothelial layers of normal RMs decreased with increasing age. In endolymphatic hydrops, cellular proliferation and decreased cellular density of a distended RM were observed, and these changes occurred more remarkably in epithelial cells. Decreased cellular density in RM was correlated to the degree of endolymphatic hydrops. These findings indicate an involvement of the epithelial cellular changes in the pathogenesis of endolymphatic hydrops. Our results suggest that cellular changes in RM may cause dysfunction of radial flow leading to ionic disturbance of endolymph, which provides a possible mechanism of hearing loss in endolymphatic hydrops.

KEY WORDS — endolymphatic hydrops, morphology, Reissner's membrane, temporal bone.

INTRODUCTION

Endolymphatic hydrops is known to be a common histologic finding in Meniere's disease,[1] and it is also found in otitis media,[2,3] labyrinthitis,[4] and otosclerosis.[5] In endolymphatic hydrops, a distention of Reissner's membrane (RM) is consistently observed. Reissner's membrane is situated between the scala media and the scala vestibuli. It is a thin membrane that consists of two cell layers: the epithelial cells, of ectodermal origin, on the surface toward the scala media; and the mesothelial cells, of mesodermal origin, on the surface toward the scala vestibuli. Reissner's membrane not only forms a barrier between the endolymphatic and perilymphatic compartments but also may be involved in transport of ions and fluids.[6]

Morphologic studies of normal RMs in humans and in animal species have been reported.[7-10] A recent study quantified the cellularity of the epithelial and mesothelial layers of RM in aged rats.[11] Quantitative morphologic study of cellularity in RM, however, has not been undertaken in normal human temporal bones and human temporal bones with endolymphatic hydrops. Cellular changes in RM may help our understanding of the etiopathogenesis of endolymphatic hydrops and may provide an index of severity of endolymphatic hydrops.

MATERIAL AND METHODS

A total of 50 temporal bones from 25 subjects who ranged in age from 2 days to 89 years were included in this study. Because it is difficult to differentiate cells of RM from those of the endosteal layer in cases of severe hydrops, cases in which RM was completely attached to the endosteal layer were excluded to ensure accuracy of cell counts. These temporal bones were divided into three groups. Group 1 included 30 normal temporal bones from 15 subjects without otopathologic histories, group 2 consisted of 6 subjects with unilateral endolymphatic hydrops, and group 3 had 4 subjects with bilateral hydrops.

All temporal bones were processed by fixation, decalcification, and celloidin embedding. Sections were cut horizontally at thicknesses of 20 μm, and every 10th section was stained with hematoxylin and eosin. Morphometric measurements were made in the basal turn of the cochlea at the level of the midmodiolar sections and the adjacent two sections. This pilot study was confined to the basal turn because controversy exists regarding apical hydrops.[12] Morphometric measurements of RM included the width and cellularity of RM. Width of RM was measured from the vestibular crest of the spiral ligament to the limbus spiralis (Fig 1). For cellularity of RM, nuclei of epithelial and mesothelial cells were counted in two ways: the number of cells for the entire width of RM and the number of cells per millimeter of RM. The average of three measurements was calculated for analysis of mean values. To determine if changes in RM were age-related, the 15 control subjects (those without otopathologic histories) were equally divided into three age ranges: 0 to

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Presented at the meeting of the American Otological Society, Inc, Palm Beach, Florida, April 28-29, 1990.

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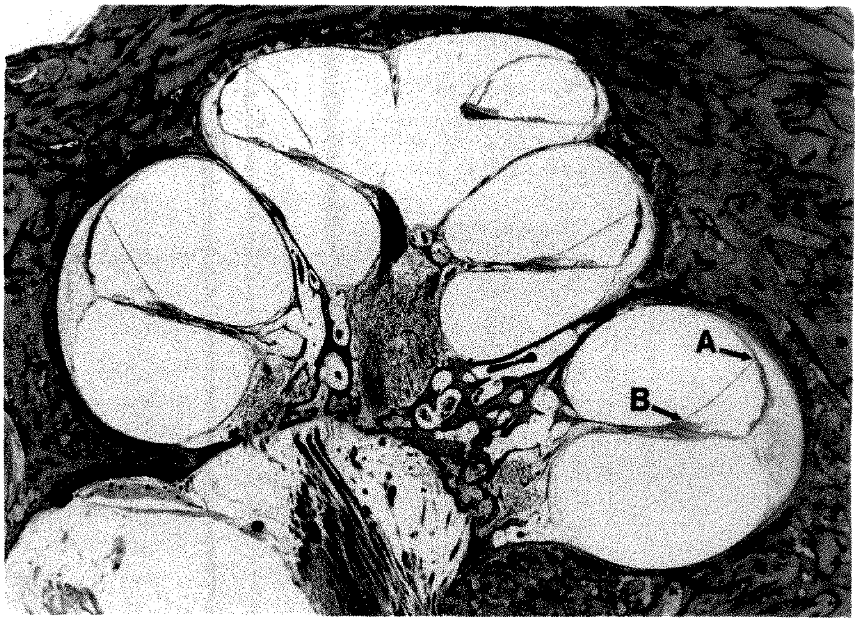

Fig 1. Midmodiolar section of normal temporal bone (H & E, original x25). Width of Reissner's membrane was measured from vestibular crest of spiral ligament (point A) to limbus spiralis (point B) in basal turn of cochlea.

10 years, 11 to 60 years, and over 60 years, and the histologic measurements of the groups were statistically compared. Changes in the organ of Corti, stria vascularis, and spiral ganglion cells were assessed for normality or abnormality.

RESULTS

In normal subjects, the cellular arrangements in RM were regular and the shapes of cells were uniform (Fig 2). Arrangements of epithelial cells in RM were more regular than those of mesothelial cells. The cellular arrangements in RM became more irregular with increasing age. Cluster formations of epithelial cells were occasionally observed in subjects in old age. In general, the appearance of the organ of Corti, stria vascularis, and spiral ganglion cells was normal.

The average width of a normal RM was 0.77 mm, and width ranged from 0.60 to 0.93 mm. The total number of cells including both the epithelial and

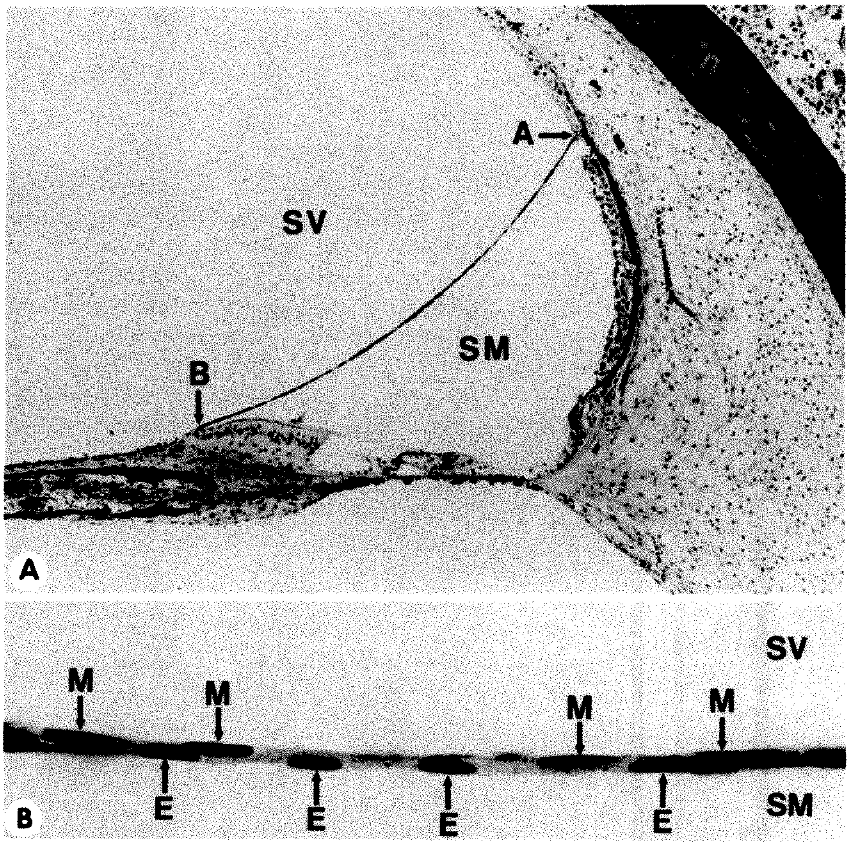

Fig 2. Normal Reissner's membrane (RM). SM — scala media, SV — scala vestibuli. A) Normal width of RM (from point A to point B) (H & E, original x130). B) Two cell layers in RM showing regular arrangements of epithelial cells (E) with occasional mesothelial cells (M) (H & E, original x1,270).

TABLE 1. NUMBER OF CELLS AND CELLULAR DENSITY OF REISSNER'S MEMBRANE

	Age Group		
	0-10 y	*11-60 y*	*60+ y*
No. of cells	45.62 ± 0.50	38.34 ± 1.65	37.77 ± 1.13
Cellular density*	59.50 ± 1.23	51.43 ± 2.26	45.72 ± 1.10

Values are mean ± SEM.

*Number of cells per high-power field.

mesothelial cells in a normal RM averaged 40.57, and ranged from 31.33 to 48.33. The ratio of epithelial cells to mesothelial cells was about 3:1. There were no differences between left and right ears in the width or number of cells of RM as determined by a *t* test. The width of RM did not change with increasing age. The number of cells and cellular density of RM (Table 1), including the epithelial and mesothelial cells, decreased with increasing age as determined by using Pearson correlation coefficients ($p < .01$).

In endolymphatic hydrops, the arrangement of epithelial and mesothelial cells in RM was irregular. Bulging of the epithelial cell layer and cluster formations of small epithelial cells were frequently observed, particularly near the stretched area of the distended RM in the mild or moderate degree of hydrops (Fig 3). In the severe degree of hydrops, the epithelial cell layer was stretched and showed wide spaces between nuclei of cells (Fig 4).

Table 2 shows quantitative measurements of the number of cells for the entire width of RM in normal subjects and in subjects with endolymphatic hydrops. The number of cells and the width of RM in normal ears were not significantly different from those in nonhydropic ears of unilateral hydrops. In ears with endolymphatic hydrops, the number of cells and the width of RM were significantly increased ($p < .01$). This cellular proliferation occurred mostly among epithelial cells.

The cellular density of RM is shown in Table 3. In unilateral hydrops, differences in cellular density between the nonhydropic ears and the hydropic ears were only significant among mesothelial cells as determined by a *t* test ($p < .05$). The cellular density of epithelial cells in RM in ears with bilateral endolymphatic hydrops was significantly lower than that in ears with unilateral hydrops, according to results of a *t* test ($p < .05$).

The severity of endolymphatic hydrops was categorized as mild, moderate, or severe according to the range of width of distended RMs (Table 4). Unilateral hydrops was mostly of mild or moderate degree, but hydrops was severe in bilateral cases. Cellular density decreased with increasing degree of hydrops. By the analysis of covariance, the correlation was found to be nearly significant ($p = .064$). In general, inner ear changes in the organ of Corti, stria vascularis, or spiral ganglion cells were not remarkable in endolymphatic hydrops, and these

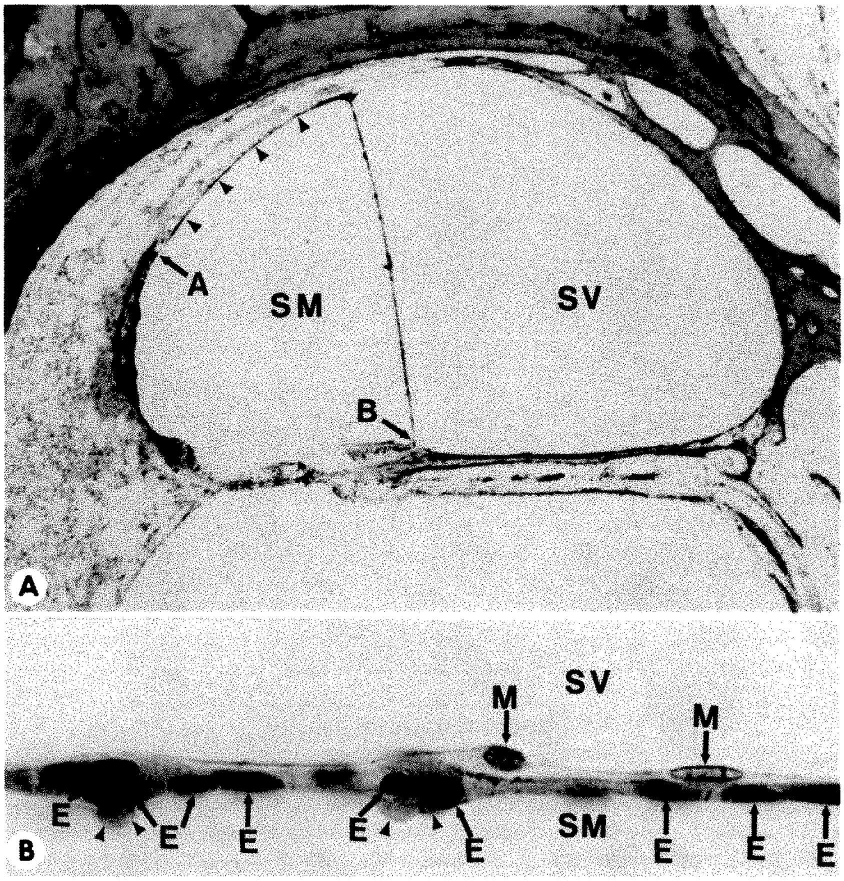

Fig 3. Reissner's membrane (RM) in mild degree of endolymphatic hydrops. SM — scala media, SV — scala vestibuli. A) Distended RM (arrowheads) attached to spiral ligament (H & E, original x90). Width of RM is from point A to point B. B) Bulging (arrowheads) of epithelial cell layer and cluster formations of epithelial cells (E) (H & E, original x1,270). Mesothelial cells (M) are occasionally seen.

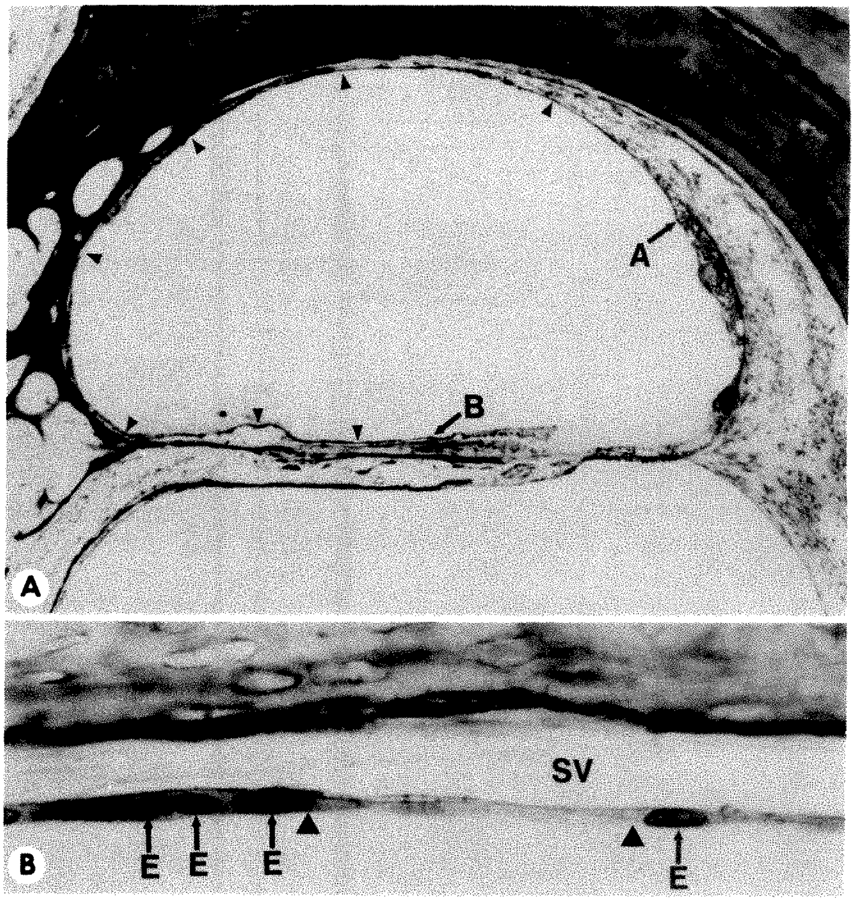

Fig 4. Reissner's membrane (RM) in severe degree of endolymphatic hydrops. A) Distended RM (arrowheads) nearly filling scala vestibuli (H & E, original x90). Width of RM is from point A to point B. B) Wide space (arrowheads) between nuclei epithelial cells (E) of RM (H & E, original x1,270). Mesothelial cells are not seen. SV — scala vestibuli.

changes were not correlated to morphologic changes in RM. There were no remarkable differences in cellular changes in RM between various causes of endolymphatic hydrops, such as otitis media, otosclerosis, or unknown causes.

DISCUSSION

It has been described that cellular arrangements in RM in normal human temporal bones become more irregular with increasing age. Johnsson,[9] using the technique of microdissection and phase-contrast examination of surface specimens, has shown that an irregular arrangement of epithelial cells is observed in RM in humans; with advancing age that configuration of cells becomes even more irregular, and many cells increase further in size. He also described vacuolization of RM in aged patients. Watanuki et al,[10] using light microscopy and surface preparation techniques, found a similar histologic finding in RM in aged patients, and stated that a remodeling of the epithelial layer of RM may occur owing to a slight change in pressure or chemical contents of fluids of the inner ear. Our findings are consistent with observations previously reported. These findings suggest that cellular changes in RM can occur as part of the aging process in humans.

Feldman,[11] in a quantitative study of RM in rats, observed a decrease in cellular density of RM in aged rats. He suggested that the decreased cellular density of RM may contribute to hearing loss in advancing age. We demonstrated that the number of cells and the cellular density in both epithelial and mesothelial layers of RM were decreased in aged human temporal bones. These results indicate that an age-related process of cellular degeneration can occur in both the epithelial and mesothelial cells of RM.

Although many studies of temporal bones using

TABLE 2. NUMBER OF CELLS FOR ENTIRE WIDTH OF REISSNER'S MEMBRANE

	Group 1 (n = 15)	Group 2 (n = 6)		Group 3 (n = 4)
		Nonhydropic Ear	*Hydropic Ear*	
Cells (No.)				
Epithelial	30.85±0.96	31.76±1.59	80.63±11.72	78.42±5.55
Mesothelial	9.72±0.38	7.41±0.99	9.75± 1.29	10.67±0.53
Total	40.57±1.30	39.18±2.52	90.55±12.06	89.10±5.76
Width (mm)	0.77±0.01	0.77±0.03	1.84± 0.22	2.28±0.14

Values are mean±SEM.

TABLE 3. CELLULAR DENSITY OF REISSNER'S MEMBRANE (NUMBER OF CELLS PER MILLIMETER)

	Group 1 (n = 15)	*Group 2 (n = 6)* Nonhydropic Ears	*Group 2 (n = 6)* Hydropic Ears	*Group 3 (n = 4)*
Cells				
Epithelial	39.56±1.34	40.61±1.21	43.11±2.15	34.46±1.38
Mesothelial	12.65±0.58	9.40±1.06	5.71±0.82	4.80±0.28
Total	52.21±1.87	50.01±2.18	48.83±2.62	39.26±1.22

Values are mean±SEM.

light microscopy have described histopathologic changes of the inner ear in Meniere's disease and labyrinthine hydrops,[12-17] only a few studies have described morphologic changes in RM. Johnsson[9] observed high cellularity of small cells in the distended RM of a specimen from a patient with severe hydrops. He suggested that a multiplication of cells could occur in the hydropic RM. Kimura et al,[18] in a study of Meniere's disease, and Shinozaki and Kimura,[19] in an experimental study, observed that the distended RM was flat, frequently lacked mesothelial cells, and showed atrophy of epithelial cells, suggesting a cellular stretching of RM in endolymphatic hydrops. Ruding et al[20] found various folds, local thickening, mesothelial defects, ruptures, and atrophy of RM in experimental endolymphatic hydrops. Albers et al[21] in an ultrastructural study of RM observed extensive gaps in the mesothelial layer together with intracellular pathologic conditions in epithelial cells, in experimental hydrops. The present study demonstrated an increased number of epithelial cells associated with an increased width of RM, but a decreased cellular density of RM in endolymphatic hydrops. These results indicate that the cellular multiplication and stretching of RM can occur together in the progression of endolymphatic hydrops.

Kimura[22] stated that the distention of the membranous labyrinth occurred first in the saccule and lower turn of the cochlea after blockage of the endolymphatic duct and sac in the guinea pig. Changes in the sensory cells, the stria vascularis, and cells of the spiral ganglion, however, were mostly effected in the apical turn. He interpreted this to mean that a stagnation of endolymphatic flow may have occurred in the narrow turn, resulting in an accumulation of metabolic waste products in the apical turn. Ruding et al[20] found that degeneration of the stria vascularis and hair cells started apically and proceeded toward the cochlear base after endolymphatic sac obstruction. We did not find any direct correlation between cellular changes in RM and changes in the organ of Corti, stria vascularis, or ganglion cells in the basal turn of the cochlea. Whether the role of RM is active or passive in the development of endolymphatic hydrops, radial as well as longitudinal flow appeared to be involved.

TABLE 4. CORRELATION BETWEEN DEGREE OF HYDROPS AND CELLULAR DENSITY

Degree of Hydrops	*No. of Ears*	*Average Width (mm)*	*Cellular Density (mean±SEM)*
Normal	30	0.77	52.21±1.87
Mild	3 (2 U + 1 B)	1.34	46.33±3.14
Moderate	5 (3 U + 2 B)	1.87	45.60±3.33
Severe	6 (1 U + 5 B)	2.65	40.01±1.64

Mild — 0.78 to 1.54 mm, moderate — 1.55 to 2.31 mm, severe — 2.32 mm and over, U — unilateral hydrops, B — bilateral hydrops.

Ruding et al[20] reported that the degree of hydrops and histopathologic changes in RM increased with increasing survival time after sac obstruction. Morizono et al,[23,24] and van Deelen et al[25] in an experimental study, reported that changes in action potential thresholds were positively related to the degree of hydrops and the postoperative interval. Although these studies correlated the degree of hydrops to changes in action potential thresholds or duration of hydrops, the relationship between the degree of hydrops and the cellular changes in RM in endolymphatic hydrops has never been quantified. In this study we observed a close correlation between the degree of hydrops and cellular changes in RM in endolymphatic hydrops. A decreased cellular density of RM can cause wide gaps between cells and a marked stretching of the distended RM. This study clearly demonstrated epithelial cellular changes in RM in endolymphatic hydrops. These changes could have been actively or passively involved in endolymphatic hydrops. A possible mechanism of hearing loss in endolymphatic hydrops is dysfunction of radial flow leading to an ionic disturbance of endolymph. Further studies will be required to clarify this concept.

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THE DEAFNESS RESEARCH FOUNDATION
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The Deafness Research Foundation's Otological Research Fellowship will be sponsored by a department of otolaryngology conducting otological research. Where a unique opportunity exists in a related discipline, the fellowship may be conducted in that discipline while maintaining liaison with the department of otolaryngology. The fellowship would be scheduled as a one-year block of time at the end of the third year of medical school, thus requiring a one-year leave of absence from the medical school curriculum. The fellowship would be funded in the amount of $10,000, plus up to $3,500 for animals and consumable supplies. Applications for 1992 funding must be received by November 15, 1991. For more information, please contact Walter A. Petryshyn, MD, Medical Director, The Deafness Research Foundation, 9 East 38th Street, New York, NY 10016; (212) 684-6556.

Ann Otol Rhinol Laryngol 100:1991

RAT AS A POTENTIAL MODEL FOR HEARING LOSS IN BIOTINIDASE DEFICIENCY

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Biotinidase deficiency is an inborn error of metabolism that is transmitted as an autosomal recessive disorder. Symptoms include hearing loss, ataxia, blindness, mental retardation, and seizures. The metabolic defect is an inability to recycle the vitamin biotin, which is an important cofactor in key enzymes. We therefore sought to develop an animal model for this disorder by inducing biotin deficiency. Rat pups were divided into control and experimental groups. Control rats were fed a normal diet whereas experimental animals were given a diet deficient in biotin. Animals from both groups underwent brain stem auditory evoked potential testing at various ages. Wave I thresholds at various ages were similar in both groups. Latencies for wave I, however, and interpeak latencies (I-IV) were prolonged in the biotin-deficient groups compared to controls. Scanning electron microscopy of the organ of Corti in biotin-deficient animals showed no significant hair cell loss. The biotin-deficient developing rat appears to acquire functional changes in the auditory brain stem. These effects may be caused by defective myelination, since biotin is important in fatty acid metabolism.

KEY WORDS — biotin, development, evoked potentials, hearing loss.

INTRODUCTION

Biotin is a water-soluble vitamin of the B-complex group. This compound acts as a prosthetic in four key enzymes involved in glucose, fatty acid, and amino acid metabolism.[1] In 1983 Wolf et al[2] demonstrated that the primary biochemical defect in patients with so-called late-onset multiple carboxylase deficiency was a lack of the enzyme biotinidase (EC3.5.1.12). This is a key enzyme in the biotin cycle that recycles biotin from protein binding sites. Biotinidase deficiency is inherited as an autosomal recessive trait.[3] Symptoms of this disorder include hearing loss, ataxia, alopecia, skin rash, hypotonia, and developmental delay, often accompanied by lactic acidosis and organic aciduria[3] (Table 1). Severe to profound bilateral sensorineural hearing loss has been reported. The purpose of the present study was to develop an animal model for this potentially devastating human condition in order to study its effects on the peripheral and central auditory system by using auditory brain stem response testing and scanning electron microscopy of the organ of Corti.

METHODS

Sprague-Dawley rats were bred locally in our vivarium. At the time of assumed date of conception, pregnant rats were placed on either a normal rat diet containing biotin (controls) or a special diet to induce biotin deficiency (experimentals). The latter is a commercially available diet containing 30% dry weight raw egg white (Teklad, Harlan, Sprague-Dawley, Madison, Wis) to accelerate biotin depletion.[4] After weaning, the respective diets were continued in rat pups from each group. The above diet has reliably induced biotin deficiency in other laboratories,[4,5] as judged by the appearance of classic physical findings of biotin deficiency[4,6] (Fig 1). Biotin deficiency was further documented by assay of plasma biotin concentrations at various ages. The

TABLE 1. CLINICAL AND BIOCHEMICAL FEATURES OF BIOTINIDASE DEFICIENCY

Seizures
Ataxia
Hypotonia
Hyperventilation, stridor, apnea
Developmental delay
Hearing loss
Visual problems (including optic atrophy)
Skin rash
Alopecia
Conjunctivitis
Fungal infection
Metabolic acidosis
Lactic acidosis
Hyperammonemia
Organic aciduria

From the Department of Surgery, Southern Illinois University, School of Medicine, Springfield, Illinois. This study was supported by the Deafness Research Foundation and National Institutes of Health/National Institute on Deafness and Other Communication Disorders (5R01DC00321). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Southern Illinois University.

Presented at the meeting of the American Otological Society, Inc, Palm Beach, Florida, April 28-29, 1990.

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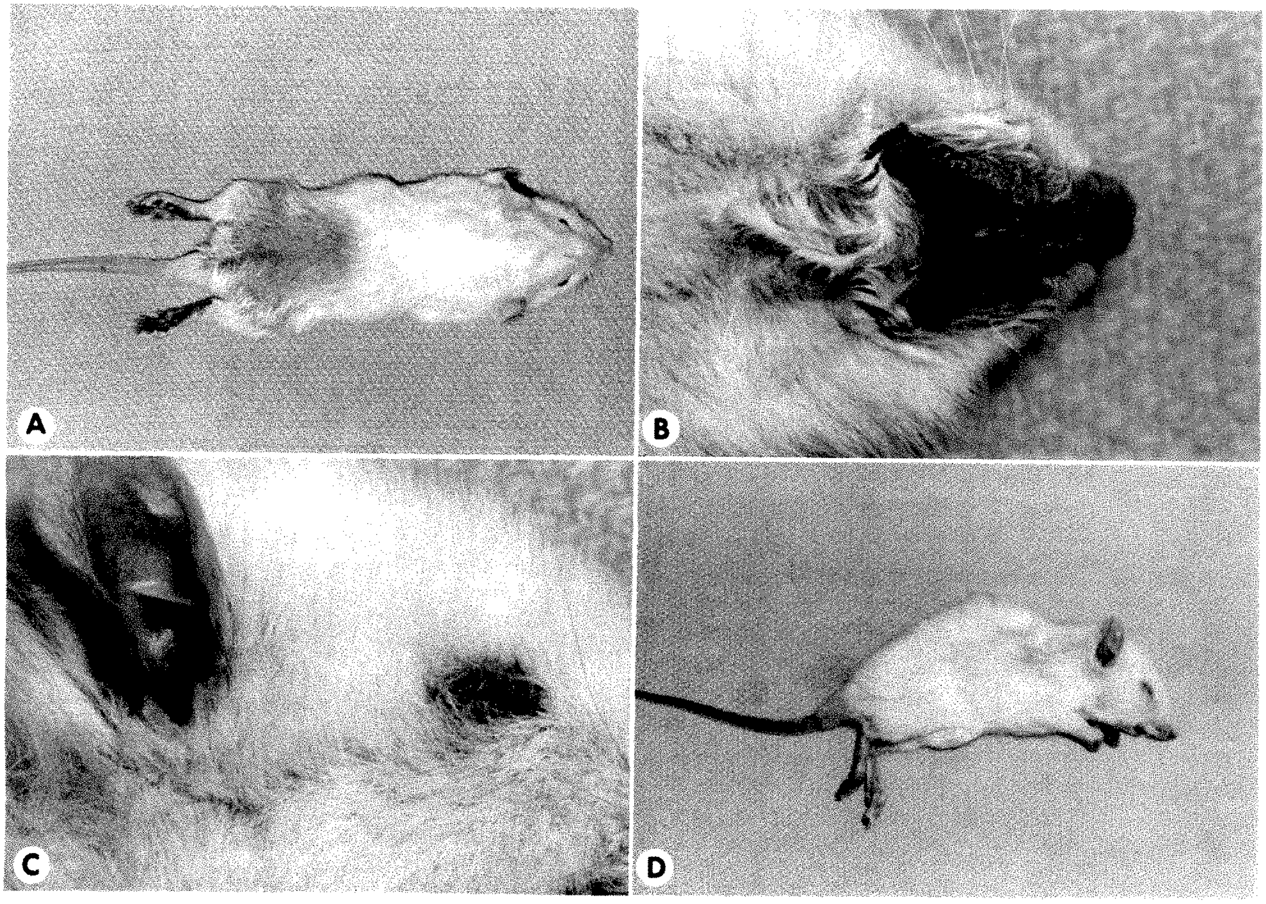

Fig 1. Biotin-deficient rats. A) Dorsal view of 25-day-old rat showing alopecia of lower back. B) Ventral view of 40-day-old rat displaying scaly patches at corners of mouth and sialorrhea. C) Close-up view of eye of 40-day-old rat demonstrating blepharitis, closure of eyelids, and "spectacled eye." D) Lateral view of 40-day-old rat displaying arching of back.

body weight of control and experimental animals was recorded because of the known adverse effects of biotin deficiency on growth.[4,7,8]

Serum Biotin Assay. Serum was obtained from rats after auditory testing. Samples were obtained by cardiac puncture. A 1:4 dilution of serum was made in 2N sulfuric acid. Tubes were covered with aluminum foil to protect them from light and they were autoclaved at 121°C at 15 psi for 30 minutes. After cooling, samples were filtered through a syringe filter. The pH was adjusted to 6.8 ± 2 by using 20% NaOH and 2N sulfuric acid. Various dilutions were used for control and biotin-deficient serum samples. Fresh solutions of biotin standards were used to make standard curves.

Lactobacillus plantarum was used as the test organism. Freeze-dried organisms were obtained from the American Type Culture Collection (Rockville, Md). An 18- to 24-hour growth of *L plantarum* in lactose broth was used to prepare the inoculum. Organisms were centrifuged, washed with sterile saline, and diluted 1:100. One drop of inoculum was added to the deproteinized serum dilutions, shaken well, and incubated protected from light for 18 to 24 hours in a water bath at 37°C.

Growth was stopped by autoclaving at 121°C at 15 psi for 5 to 10 minutes. The slit width of a spectrophotometer was adjusted by using an inoculum blank. Optical density at 620 nm was measured by using aliquots from each sample. The values for unknown samples were extrapolated from a standard curve. Each sample was run in triplicate.[9,10]

Brain Stem Auditory Evoked Potentials. Control and experimental animals, ages 1 to 45 postnatal days, were anesthetized by using 5% chloral hydrate, 7.6 mL/kg intraperitoneally. Subdermal electrodes were placed at the vertex (active), at the nose (reference), and over the neck muscles (ground). Body temperature was maintained at 37°C by using an animal warming blanket. Brain stem auditory evoked potentials (BAEPs) were recorded in response to free-field binaural stimuli generated by a tweeter suspended 8 cm above the vertex in a double-walled soundproof booth (Industrial Acoustics Corp). Auditory stimuli consisted of 100-microsecond clicks. Clicks were presented at a rate of 5 per second. The resulting BAEP waveform was amplified by using a W-P Instruments DAM 60 preamplifier, further amplified using a Tektronix oscilloscope, and averaged 512 times on a Nicolet 1170 signal averager for a total amplification of 40,000

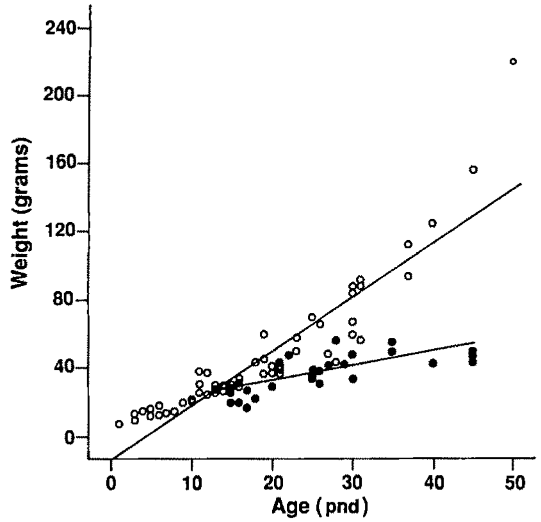

Fig 2. Weight in grams for control (open circles) and biotin-deficient (filled circles) rats of various ages. pnd — postnatal days.

times. Permanent records were made on an x-y plotter. Clicks were previously calibrated to a maximum output of 90 dB sound pressure level by using a Bruel & Kjaer impulse precision sound level meter with a 6-mm microphone placed 8 cm below the transducer. Intensity series were recorded from 10 dB subthreshold to 30 dB suprathreshold in 10-dB steps.

Threshold was determined as the lowest intensity at which reproducible waveforms could be elicited. Latencies were measured from the onset of the stimulus to the positive maxima of each wave, with a correction for the travel time from the speaker to the ear.[11] Positive wave amplitudes were measured by triangulation.[11] Control and experimental groups were statistically compared by using the analysis of variance.

Scanning Electron Microscopy. After BAEP recordings were completed, animals were given an intraperitoneal injection of Sleepaway (a concentrated sodium pentobarbital and alcohol solution) 2 mL/kg. Animals were then decapitated and the auditory bullae were removed. The cochleae were dissected out. A small hole was made in the apex of each cochlea and the oval and round windows were opened. The cochleae were perfused with 2.5% glutaraldehyde in 100 mmol/L phosphate buffer, through the perilymphatic spaces, by using a small syringe connected to a tube that fit over the apex of the cochlea. After perilymphatic perfusion, the cochleae were immersed in 2.5% glutaraldehyde and rotated for 3 hours and refrigerated overnight. The following day, cochleae were rinsed with 100 mmol/L phosphate buffer and post-fixed with 1.5% osmium tetroxide for 2 hours.

Post-fixed cochleae were rinsed in phosphate buffer. The bony capsule was dissected away by using a dental drill and a small pick, exposing the lateral spiral ligament of each turn. The lateral wall was cut away with a small blade, while Reissner's membrane and the tectorial membrane were pulled away by using fine jeweler's forceps. The remaining intact organ of Corti and modiolus were rinsed in deionized, distilled water and immersed in 0.8% thiocarbohydrazide for 30 minutes. The tissue was rinsed again and placed in 1.0% aqueous osmium tetroxide for 30 minutes, followed by a final rinse. This is referred to as the OTO (osmium-thiocarbohydrazide-osmium) method and is an abbreviated version of the TOTO (thiocarbohydrazide-osmium-thiocarbohydrazide-osmium) method used by Davies and Forge.[12] Cochleae were dehydrated in ethyl alcohol and critical point dried, after which they were mounted on aluminum stubs and sputter coated with approximately 20 nm of gold. These samples were then viewed on a Hitachi S 500 scanning electron microscope and photographed. Each half turn of each cochlea in both groups was evaluated.

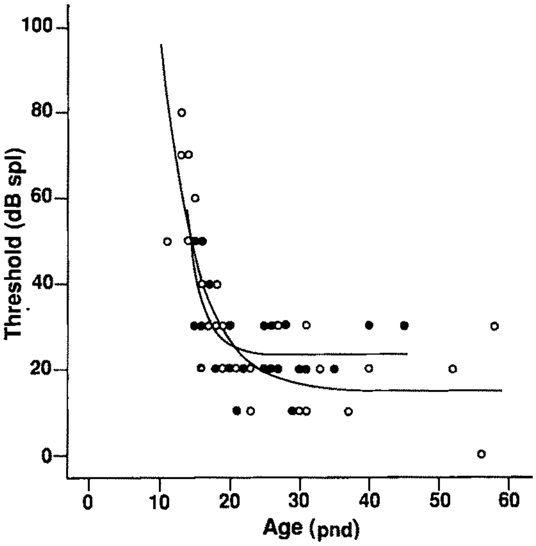

Fig 3. Brain stem auditory evoked potential thresholds to click stimuli at various ages in control (open circles) and biotin-deficient (filled circles) rats. pnd — postnatal days.

RESULTS

Skin Changes. Experimental animals demonstrated typical skin changes described for "egg white injury." Alopecia of the lower back (Fig 1A) occurred at 25 days of age. Scaly patches at the corners of the mouth (Fig 1B) and severe blepharitis leading to closure of the eyelids (Fig 1C) were exhibited by the biotin-deficient rats at 40 days. In addition, an arched back (Fig 1D), which can lead to a kangaroo gait, was also seen at 40 days after birth. Various other signs, such as lessened activity, excessive salivation (Fig 1B), rough coat, hematuria, and erythema of the feet (Fig 1A), were noted. Although there was some tendency for the "spectacled eye" condition to develop, blepharitis was more pronounced (Fig 1C). These findings have been summarized previously by other authors investigating the skin effects of biotin deficiency.[4,6]

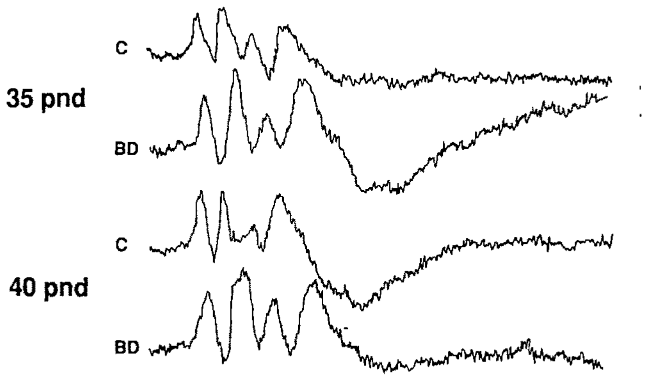

Fig 4. Pairs of brain stem auditory evoked potential waveforms following click stimulation at 10 dB suprathreshold in control (C) and biotin-deficient (BD) rats at 35 and 40 postnatal days (pnd) of age.

Growth. Growth was drastically affected in the biotin-deficient rats. Whereas the control rats had a rapid growth pattern, the biotin-deficient rats reached a plateau at about 30 days of age (Fig 2).

Biotin Levels. Biotin levels were extremely low in nearly all animals on the biotin-deficient diet, (0.63 ng/mL compared to 5.13 ng/mL in control animals), confirming that biotin deficiency was successfully produced.[9] These levels are comparable to those previously reported by Mock et al[5] in normal and biotin-deficient rats.

BAEP Findings. The mean threshold response for biotin-deficient rats did not differ from that of controls (Fig 3). Analysis of the waveforms, however, did show differences in the latencies (Fig 4). The brain stem transmission time for clicks, defined as the time interval between wave IV and wave I,[13] was significantly prolonged in the biotin-deficient animals (Table 2).

Scanning Electron Microscopy. The organ of Corti in the developing rat undergoes a series of maturational changes.[14,15] An adult-like appearance of the surface anatomy of the organ of Corti of the rat appears by day 16 in the basal turn and by the end of the third postnatal week in the apex.[14,15]

Control animals were found to have a mature, adultlike appearance of the stereocilia and cuticular plate from the base to the apex at both 25 and 40 days of age (Fig 5). Kinocilia, which are present at an earlier age, are no longer seen at these ages.

Experimental animals, which were deficient in biotin, were found to have no significant difference in the surface anatomy of the inner and outer hair cell stereocilia and cuticular plates compared with age-matched controls (Fig 6). Therefore, the anatomic findings on scanning electron microscopy confirm the physiologic results.

No significant alterations of BAEP thresholds were found among biotin-deficient animals compared with controls. On the other hand, wave I latency and interpeak latencies for BAEP were prolonged in the biotin-deficient group. These findings suggest that biotin deficiency resulted in pathologic or pathophysiologic changes in the auditory brain stem structures responsible for controlling central auditory transmission.

DISCUSSION

The results of this study suggest that biotin deficiency in developing rats produces a prolongation of

TABLE 2. BRAIN STEM AUDITORY EVOKED POTENTIAL LATENCIES

	Control			*Biotin-Deficient*			
Age (postnatal d)	*Mean (ms)*	*SD*	*n*	*Mean (ms)*	*SD*	*n*	*p*
Wave I							
11-20	1.55	0.19	17	1.71	0.28	9	<.090
21-30	1.26	0.12	13	1.39	0.09	13	<.006
31-45	1.25	0.08	11	1.38	0.05	6	<.004
Interwave I-IV							
11-20	3.73	0.67	17	4.80	0.64	9	<.001
21-30	3.22	0.34	13	3.62	0.24	13	<.002
31-45	2.92	0.38	11	3.34	0.08	6	<.005
Interwave I-II							
11-20	1.22	0.05	17	1.47	0.26	9	<.024
21-30	1.02	0.12	13	1.09	0.11	13	<.549
31-45	0.97	0.10	11	1.06	0.11	6	<.142
Interwave I-III							
11-20	2.25	0.47	14	2.94	0.41	9	<.002
21-30	1.91	0.20	13	2.22	0.16	13	<.001
31-45	1.76	0.16	11	2.05	0.05	6	<.001
Interwave II-III							
11-20	1.07	0.41	14	1.47	0.30	9	<.020
21-30	0.89	0.12	13	1.13	0.16	13	<.001
31-45	0.78	0.08	11	0.99	0.13	6	<.001

Click stimulus at 30 dB suprathreshold. Transmission time of 0.23 millisecond subtracted.

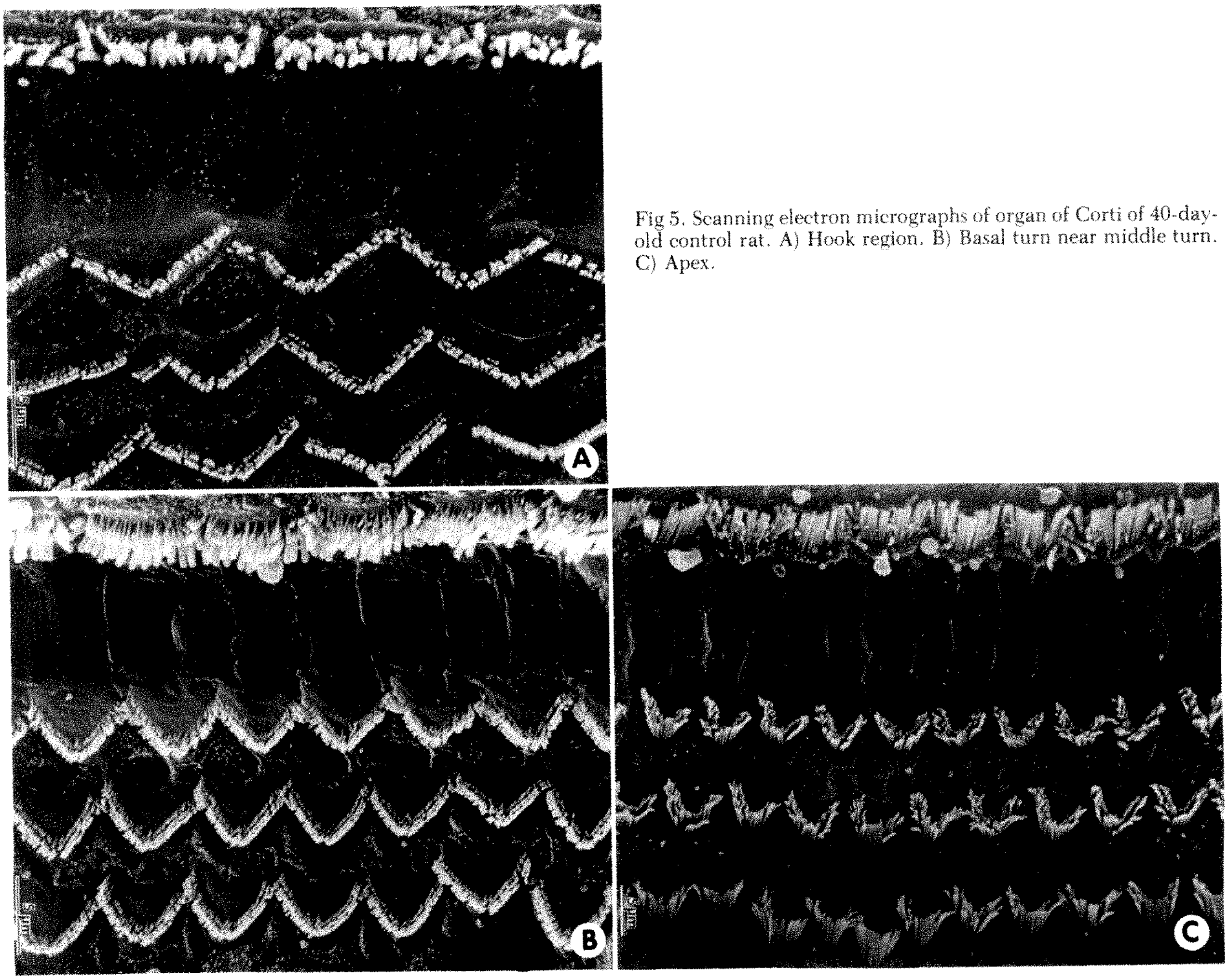

Fig 5. Scanning electron micrographs of organ of Corti of 40-day-old control rat. A) Hook region. B) Basal turn near middle turn. C) Apex.

interpeak latencies of the BAEP with no discernible effect on the BAEP threshold. These findings are corroborated by the lack of alteration of structure of the organ of Corti on scanning electron microscopy. Biotin deficiency produces characteristic changes in growth and the appearance of the skin and hair of experimental animals on biotin-deficient diets. The fact that biotin deficiency was produced was supported by measurement of biotin blood levels by using a microbiological method.

In this study we have used the developing rat to investigate the effects of biotin deprivation during development of auditory function. This model is the best current one for biotin deficiency[5] and is applied in this study as a potential model for human biotinidase deficiency.

Biotinidase deficiency in humans is a newly described form of metabolic deafness. Other serious complications of this enzyme deficiency can include blindness, seizures, mental retardation, susceptibility to infection, metabolic ketolactic acidosis, and organic aciduria.[3] Screening tests for biotinidase deficiency have been carried out in a number of countries[16-18] and in a number of areas within the United States.[2,3,19] Of 1 million infants screened, 14 infants with severe and 8 infants with partial biotinidase deficiency have been identified[3,20] — an incidence that approaches 1:40,000. Since the enzyme activity in blood is stable for at least 18 months at room temperature, samples may be sent to testing laboratories for analysis. Such screening is extremely important, because early treatment with high doses of biotin may reverse many of the complications of biotinidase deficiency.[3]

Biotinidase deficiency in humans is an inborn error of metabolism that is transmitted by an autosomal recessive trait.[21] It is characterized biochemically by an inability of the affected individual to recycle biotin. Biotin normally becomes conjugated to amino acids and proteins, so that it is unavailable for its important role in carboxylation reactions. In normal individuals biotin is readily and rapidly recycled in its free form. The lack of biotinidase in afflicted persons causes a rapid reduction of free biotin levels in blood and tissues, producing biotin deficiency. This would tend to reduce the activity of key biotin-dependent enzymes in metabolism. These enzymes include acetyl coenzyme A carboxylase, pyruvate carboxylase, propionyl coenzyme A carboxylase, and 3-methyl crotonyl coenzyme A car-

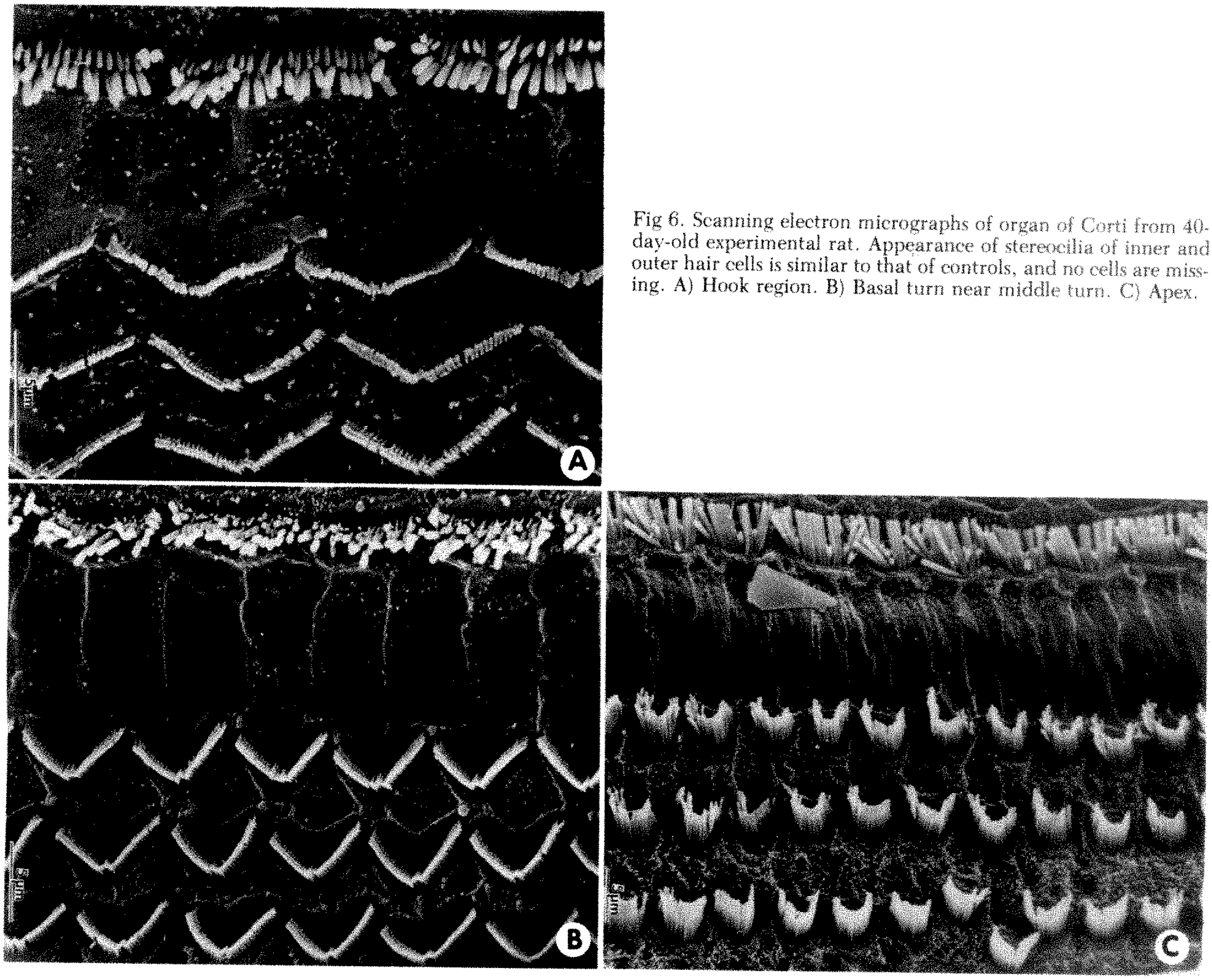

Fig 6. Scanning electron micrographs of organ of Corti from 40-day-old experimental rat. Appearance of stereocilia of inner and outer hair cells is similar to that of controls, and no cells are missing. A) Hook region. B) Basal turn near middle turn. C) Apex.

boxylase.[21-23] These enzymes play a key role in lipid metabolism, gluconeogenesis, and catabolism of essential amino acids.[21,23,24] The reduction of the activity of these enzymes by biotin deficiency could then result in altered lipid metabolism and also some effects on protein metabolism. This would have a significant impact on lipid-containing tissues with a high rate of turnover, such as the developing nervous system. This in turn could retard the myelination process in developing auditory structures, such as the auditory nerve and auditory brain stem pathways. The most rapid rate of myelination in the rat occurs at 20 postnatal days of age.[25] Furthermore, Shah et al[26] have shown a correlation between developmental changes in the latencies of early auditory evoked potentials and the lipid composition of the inferior colliculus. The rapid decline in interpeak latencies (waves II-IV) between the 15th and 26th postnatal days is accompanied by a corresponding increase in the inferior collicular concentration of cerebroside, which is exclusively a myelin lipid. These results suggested a specific correlation between the latency changes of far-field potentials and myelination.[26] Biotin deficiency could result in delayed neural conduction time, manifesting as prolonged brain stem transmission time, as was found in the present study. Indeed, hypomyelination has been described on computed tomographic scan or magnetic resonance imaging scan in humans with biotinidase deficiency,[21] and autopsy reports of patients dying with biotinidase deficiency have revealed defective myelination in the brain.[3] Furthermore, normal rat brain oligodendrocytes have a higher concentration of biotin than other brain cells. This endogenous biotin may play a key role in myelination, since the oligodendrocyte generates large quantities of lipid for myelin production.[27] Proof of these hypotheses would require a detailed study of myelination patterns of the eighth nerve and auditory brain stem pathways of normal compared to biotin-deficient rats, which we plan to do in the next phase of the study.

SUMMARY

1. We have successfully produced biotin deficiency in the developing rat.
2. Rats with biotin deficiency develop characteristic skin changes.
3. Auditory brain stem response thresholds do not differ between biotin-deficient and control rats at similar ages.
4. However, BAEP latencies are prolonged in bio-

tin-deficient rats compared with controls.

5. The cochlear hair cells appear normal by scanning electron microscopy.
6. The above abnormalities may be caused by a disorder of auditory brain stem structures, such as defective myelination.

ACKNOWLEDGMENT — Dawn Konrad assisted in portions of this study.

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SAN FRANCISCO OTOLOGY UPDATE — 1991

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Ann Otol Rhinol Laryngol 100:1991

TRANSFORMING GROWTH FACTOR BETA: DOES IT DIRECT OTIC CAPSULE FORMATION?

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Interactions between the epithelium of the otocyst and surrounding periotic mesenchyme direct the formation of the capsule of the mammalian inner ear. In the present study, we have characterized the temporal-spatial distribution of transforming growth factor beta 1 (TGF-β1) in the epithelial and mesenchymal tissues that compose the inner ear between 10 and 14 days of embryonic development. In addition, using high-density cultures of periotic mesenchyme to model otic capsule formation, we have demonstrated that exogenous TGF-β1 can modulate otic chondrogenesis by acting as either an enhancer or a suppressor of this process. Our immunohistochemical and in vitro results suggest a paracrine action for this growth factor in modulation of epithelial-mesenchymal tissue interactions and otic morphogenesis.

KEY WORDS — chondrogenesis, growth factor, otic capsule formation, otocyst, periotic mesenchyme.

INTRODUCTION

Morphogenesis of the capsule of the inner ear is dependent upon interactions between the epithelial anlage of the membranous labyrinth (otocyst) and its associated periotic mesenchyme. Modulation of the interactions between these two tissues, in particular by enzymatic disruption of mesenchyme integrity,[1] reduction in mesenchyme volume,[2] or ablation of the otocyst,[3] results in significant developmental defects, including total absence of capsule formation. An essential interrelationship between periotic mesenchyme and otic epithelium has been suggested to regulate the temporal-spatial pattern of capsule chondrogenesis.[4] Consistent with this hypothesis are the results of recent studies in micromass cultures, in which direct evidence is provided for a twofold function of otic epithelium during otic capsule formation.[5] Acting first to initiate chondrogenesis in early periotic mesenchyme, otic epithelium changes its role to suppressor of this process at a developmental stage corresponding to perilymphatic space formation and sculpting of the presumptive otic capsule.

Transforming growth factor beta (TGF-β) is a signal polypeptide that regulates growth and differentiation of many cell types, including mesenchymal cells.[6,7] The temporal-spatial localization of TGF-β1 at sites of active morphogenesis in the developing mouse embryo[8] suggests an important role for this growth factor during embryonic development, particularly during epithelial-mesenchymal tissue interactions. Correlation of TGF-β1 messenger RNA expression in a variety of differentiating epithelia, such as dental epithelium and basal epithelium in the developing whisker follicle,[9] with the expression pattern of TGF-β1 polypeptide in underlying mesenchymal structures[8] identifies TGF-β1 as a possible paracrine regulator of underlying mesenchyme during morphogenesis. These results, in addition to the striking modulation of chondrogenesis by TGF-β1 in several chondrifying tissues,[10] led us to investigate a role for TGF-β1 in mediation of the epithelial-mesenchymal interactions that direct otic capsule formation.

In the present study, we demonstrate the temporal-spatial patterns of TGF-β1 distribution in both epithelial and mesenchymal tissues in the developing inner ear at 10, 12, and 14 days of embryonic development, a period in which epithelial-mesenchymal tissue interactions are most active during development of the inner ear. Second, we show the in vitro effects of TGF-β1 on capsule chondrogenesis by using micromass cultures of periotic mesenchyme to model otic capsule formation.

MATERIALS AND METHODS

Experimental Animals. Hybrid CBA/C57 BL6 mouse embryos were obtained by crossmating CBA-J and C57 BL6-J mice (National Cancer Institute). The vaginal plug method was used to estimate gestational age, with the day of plug occurrence designated as gestational day (gd) 1. Gravid females were painlessly killed by cervical dislocation and their uteri were placed into Dulbecco's phosphate-

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Presented at the meeting of the American Otological Society, Inc, Palm Beach, Florida, April 28-29, 1990.

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TABLE 1. IMMUNOLOCALIZATION OF TGF-β1 IN DEVELOPING MOUSE INNER EAR

Embryo Age (gestational days)	*Epithelium*		*Mesenchyme Matrix*	
	Vestibule	*Auditory*	*Vestibule*	*Auditory*
10	2+	2+	1+	1+
12	1+	2+	3+, 2+*	2+,1+*
14	2+	2+	0, 4+*	0, 4+*

Scores are relative stain intensity on a scale of 1+ to 4+, judged subjectively.

TGF-β1 — transforming growth factor beta.

*Chondrogenic mesenchyme and perilymphatic space mesenchyme, respectively.

TABLE 2. EFFECTS OF TGF-β1 ON S-GAG ACCUMULATION IN CULTURES OF PERIOTIC MESENCHYME

Age at Culture (gestational days)	*TGF-β1-Positive*	*Control*
10.5	0.165±0.027	0.020±0.006
12.0	1.066±0.242	0.456±0.059
14.0	0.107±0.055	0.498±0.053

S-GAG accumulation was assayed by spectrophotometric quantitation of matrix-bound Alcian blue stain (pH 1.0). Recorded values indicate average optical density (±SD) for five cultures per experimental group.

TGF-β1 — transforming growth factor beta, S-GAG — sulfated glycosaminoglycans.

buffered saline (PBS). Embryos were staged by a combination of somite count and external features.[11]

Immunohistochemistry. Hybrid CBA/C57 BL6 mouse inner ear specimens from embryos of 10 to 14 gd were fixed in methacarn fixative,[12] dehydrated, and embedded in paraffin (Surgipath) at 59°C. Specimens were sectioned at 5- to 7-μm thickness and collected on alcohol-cleaned, uncoated slides. Two polyclonal antibodies raised against synthetic peptides corresponding to the first 30 amino acids of mature TGF-β1 (courtesy of Drs K. Flanders and M. Sporn, Laboratory of Chemoprevention, National Cancer Institute) were used as primary antibodies. These antibodies give distinct staining patterns for the presence of intracellular (anti-LC) and extracellular (anti-CC) TGF-β1.[13,14] Nonspecific binding was prevented by preincubation with normal swine serum. Sections were incubated with primary antibody (0.05 mg/mL) at 4°C overnight in a humidified chamber. Control specimens were processed by preincubation with nonimmune serum. In some specimens, testicular hyaluronidase (Sigma H3884) at a concentration of 1 mg/mL in 0.1 mol/L sodium acetate (pH 5.5) with 0.85% NaCl (30 minutes at 37°C) was used. Following a peroxidase-antiperoxidase reaction (DAKO), specimens were counterstained with Mayer's hematoxylin (Sigma). Specimens were mounted in Crystalmount (Biomedia) with final mounting in Permount (Fisher Scientific). Tissue distribution of TGF-β1 was subjectively evaluated by the density of the peroxidase reaction product, with relative stain intensity rated on a scale of 1+ to 4+. Analysis of cell density in regions of immunostain deposition was determined by nuclei counts per unit area by using a mask placed over photomicrographs of the area of stain deposition.

Micromass Culture. Otocysts were excised with their associated periotic mesenchyme from embryos of 10.5, 12, and 14 gd. Mesenchyme was dissected free of epithelial tissue and cultured by means of modifications of the micromass technique.[5,15] Briefly, mesenchyme was dissociated with 0.05% trypsin in Hanks' balanced salt solution without calcium and magnesium for 1.5 minutes at room temperature. Cells were resuspended in Ham's F-12 media (Gibco) supplemented with 10% fetal bovine serum (Gibco) at a density of 2.5 x 10^7 cells per milliliter. Ten-microliter droplets of cell suspension (2.5 x 10^5 cells per well) were placed in the centers of wells in a 24-well tissue culture plate (Costar 3424). After an incubation period of 1 hour at 37°C, 1 mL of medium was added to each well. All cultures were then reincubated and grown in a humidified 5% CO2 atmosphere at 37°C for the duration of the culture period. Prior to cell condensation formation, or 18 hours after plating the cell suspension, 1 mL of medium containing TGF-β1 peptide (a gift of Drs K. Flanders and M. Sporn, Laboratory of Chemoprevention, National Cancer Institute) at a concentration of 1 ng/mL was added to cultures prepared from 12- or 14-gd mesenchyme for a period of 24 hours. These 12- and 14-gd growth factor–treated cultures were then returned to the control culture medium for the rest of the culture period. Exogenous TGF-β1 (1 to 10 ng/mL) was introduced to 10.5-gd cultured mesenchyme on the initial day of culture and maintained for the duration of the culture period. Control cultures were maintained in media without the addition of exogenous growth factor. Cultures were monitored daily by phase-contrast microscopy on an Olympus CK2 inverted microscope. Chondrogenic foci were identified at low magnification by their characteristic cell packing and orientation.

Quantitative Alcian Blue Staining of Micromass Cultures. After a period of 7 days in micromass cultures, cultures were fixed for 5 minutes with a solution of 10% formalin and 0.5% cetylpyridinium chloride at room temperature. Cell layers were washed with a 3% acetic acid solution adjusted to pH 1.0 with HCl and stained overnight with a 0.5% solution of Alcian blue 8GX (Sigma) in 0.1N HCl (pH 1.0). To remove unbound stain, cell layers were washed twice with 3% acetic acid solution (pH 1.0). Matrix-bound stain was extracted overnight at 4°C with 8 mol/L guanidine hydrochloride and measured by spectrophotometric quantitation using a Cambridge Technology, Inc, microplate reader equipped with a 600-nm-wavelength filter.

RESULTS

Immunohistochemical Localization of TGF-β1. We analyzed inner ear specimens for each gesta-

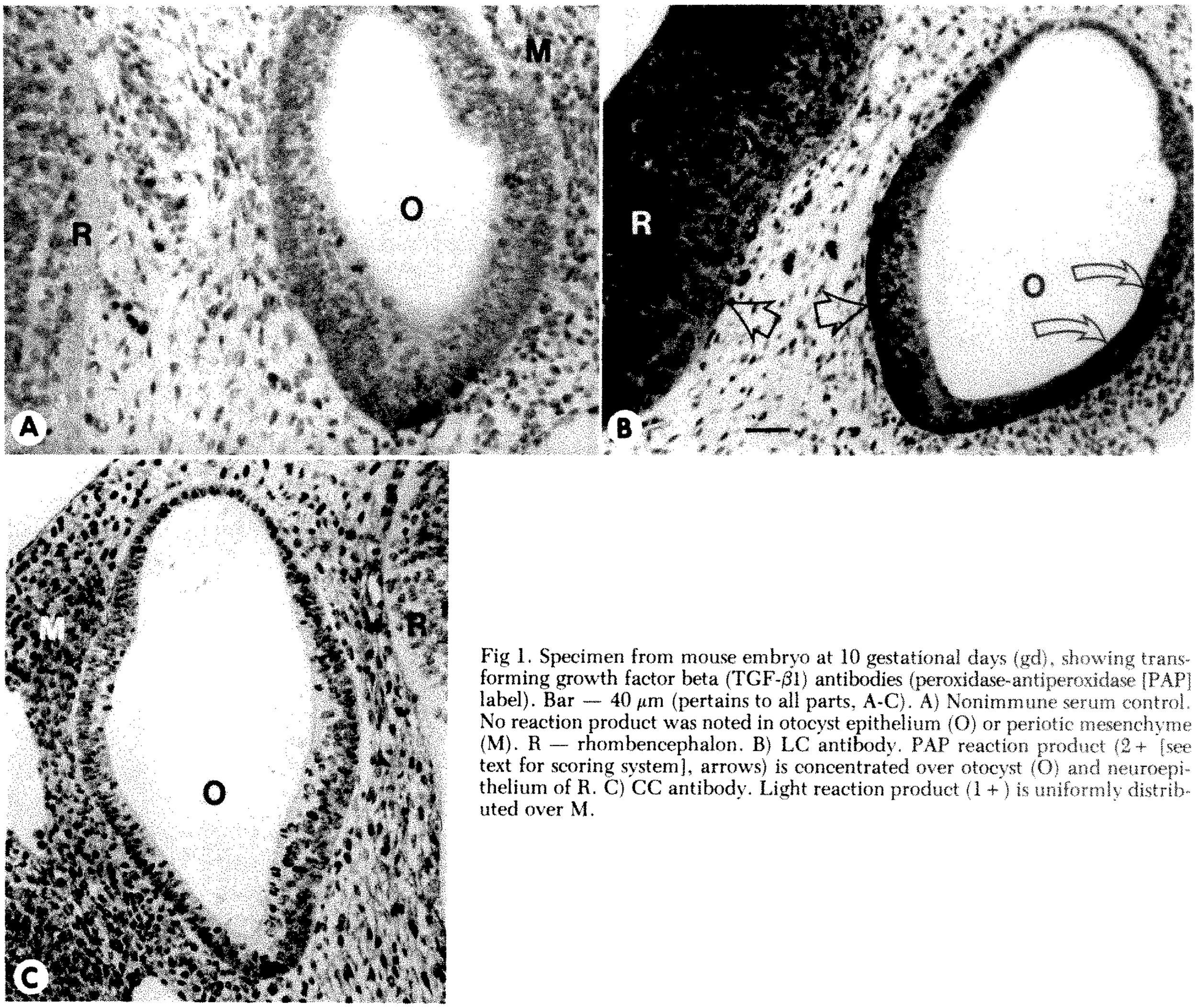

Fig 1. Specimen from mouse embryo at 10 gestational days (gd), showing transforming growth factor beta (TGF-β1) antibodies (peroxidase-antiperoxidase [PAP] label). Bar — 40 µm (pertains to all parts, A-C). A) Nonimmune serum control. No reaction product was noted in otocyst epithelium (O) or periotic mesenchyme (M). R — rhombencephalon. B) LC antibody. PAP reaction product (2+ [see text for scoring system], arrows) is concentrated over otocyst (O) and neuroepithelium of R. C) CC antibody. Light reaction product (1+) is uniformly distributed over M.

tional age studied (isolated from six embryonic mice per stage), and little variability (ie, less than one-half unit) in staining was present. We determined that TGF-β1 is transiently expressed in otic epithelial cells during capsule morphogenesis (Table 1). Intracellular expression of TGF-β1 is first observed in 10-gd inner ear specimens, in which immunostaining (2+ on the relative staining intensity scale) localizes over the neuroepithelium of the rhombencephalon and the epithelium of the otocyst (Fig 1B). At 12 gd, TGF-β1 is expressed a second time, with the densest immunostaining being localized over the epithelium of the developing cochlear duct (2+), and not over the vestibular (1+) epithelium (Fig 2B). Expression of intracellular growth factor persists until 14 days of embryonic development, when otic morphogenesis is essentially complete. Staining intensity is then greatest (2+) over the epithelium of the utricle, saccule (Fig 3B), and cochlear duct (Fig 4B). Comparisons with tissues preincubated with nonimmune serum (control specimens) are provided in Figs 1A, 2A, 3A, and 4A.

Transforming growth factor beta is present in the extracellular matrix of the periotic mesenchyme from 10 gd through 14 gd. Just prior to mesenchymal aggregation at 10 gd, a uniformly light immunostaining (1+) localizes over the matrix of the loosely organized cephalic mesenchyme that will form the otic capsule (Fig 1C). In specimens of 12 gd, staining intensity is greatest (3+) over the matrix in the vestibular periotic mesenchyme lateral to the anlage of the horizontal semicircular duct (Fig 2C). A comparison of cell densities between this area of densest immunostaining and an area of moderate staining in the mesenchyme lateral to the anlage of the cochlear duct (Fig 5) demonstrates equivalent cell numbers. Therefore, stain density cannot be a function of cell density. By 14 gd, extracellular growth factor (4+) is localized over the matrix of connective tissue in the area of the developing perilymphatic spaces in both the auditory receptors (Fig 4C) and vestibular receptors (Fig 3C).

Effects of TGF-β1 on Periotic Mesenchyme Cultures. High-density cultures of periotic mesenchyme (Fig 6) of 10.5, 12, and 14 gd were prepared. Twelve mouse embryos were used per micromass culture of 10.5 gd, 10 mouse embryos per culture of 12 gd, and 8 mouse embryos per culture of 14 gd.

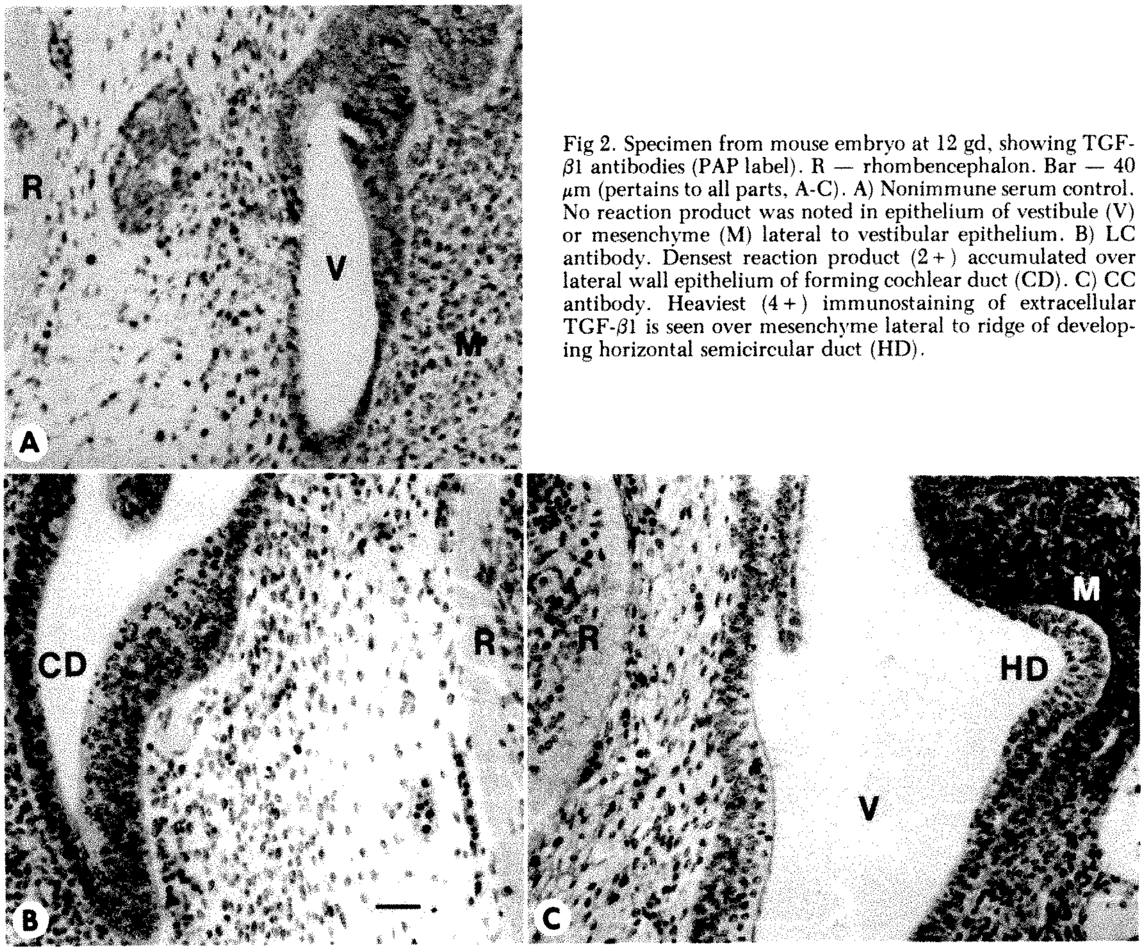

Fig 2. Specimen from mouse embryo at 12 gd, showing TGF-$\beta 1$ antibodies (PAP label). R — rhombencephalon. Bar — 40 μm (pertains to all parts, A-C). A) Nonimmune serum control. No reaction product was noted in epithelium of vestibule (V) or mesenchyme (M) lateral to vestibular epithelium. B) LC antibody. Densest reaction product (2+) accumulated over lateral wall epithelium of forming cochlear duct (CD). C) CC antibody. Heaviest (4+) immunostaining of extracellular TGF-$\beta 1$ is seen over mesenchyme lateral to ridge of developing horizontal semicircular duct (HD).

After a period of several days in high-density culture, precartilage mesenchyme differentiates into cartilage and accumulates an extracellular matrix containing highly sulfated glycosaminoglycans (S-GAG) that bind Alcian blue stain at pH 1.0.[16] Matrix-bound Alcian blue stain can therefore be used as an index of chondrification. After a culture period of 7 days, representative micromass cultures of periotic mesenchyme were fixed and stained with alcian blue (pH 1.0) and spectrophotometrically quantitated for matrix-bound stain.

Because previous studies have indicated that isolated periotic mesenchyme of 10.5 gd does not differentiate into cartilage in culture,[5] it was of interest to determine whether TGF-$\beta 1$ can act as an initiator of otic capsule chondrogenesis. A total of 10 high-density cultures of 10.5-gd periotic mesenchyme were prepared; 5 cultures were exposed to exogenous growth factor 1 hour after plating of the cell suspension, while the other 5 served as controls. Following just a 24-hour period of exposure to TGF-$\beta 1$ (1 ng/mL), a striking increase in cell packing was readily observed in the cultures exposed to growth factor as compared to control cultures. The mesenchymal cells did not develop chondrogenic foci during the 7-day culture period. However, results of spectrophotometric quantitation of bound Alcian blue stain indicated that 10.5-gd periotic mesenchyme, cultured in the presence of TGF-$\beta 1$, begins to accumulate an extracellular matrix containing S-GAG (Table 2). In the presence of higher concentrations of exogenous growth factor (5 or 10 ng/mL), S-GAG accumulation was only slightly increased (data not shown). Furthermore, increased cell packing and S-GAG accumulation did not occur if TGF-$\beta 1$ was not added on the initial day of cell plating or was not present for the duration of the culture period.

Cultured 12- to 14-gd periotic mesenchyme typically forms chondrogenic foci that accumulate a cartilage-like matrix containing S-GAG.[5] Addition of TGF-$\beta 1$ (1 ng/mL, day 1) to five high-density cultures of 12-gd periotic mesenchyme resulted in an increase in bound Alcian blue stain, and therefore S-GAG accumulation, of 57% (Table 2) as compared to control cultures. In striking contrast, suppression of chondrogenesis resulted in cultured 14-gd mesenchyme following a 24-hour exposure to exogenous TGF-$\beta 1$ (1 ng/mL, day 1). Sulfated glycosaminoglycan accumulation, as indicated in Table 2 by a dramatic decline in bound Alcian blue stain, was 72% of that of controls (Table 2). Concentrations of TGF-$\beta 1$ as low as 0.5 ng/mL (but not as high as 2 ng/mL) resulted in enhancement or suppression of S-GAG accumulation in cultured 12- or 14-gd periotic mesenchyme, respectively, but to a

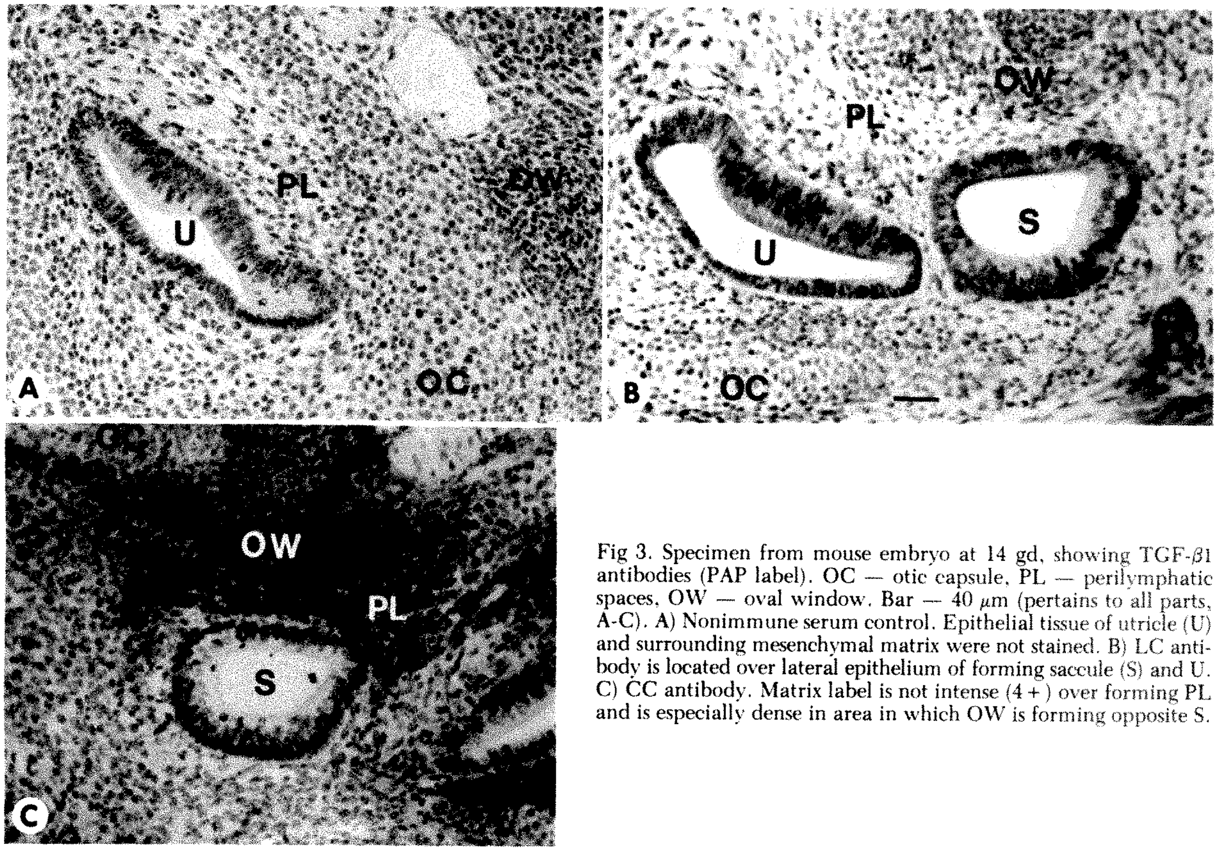

Fig 3. Specimen from mouse embryo at 14 gd, showing TGF-β1 antibodies (PAP label). OC — otic capsule, PL — perilymphatic spaces, OW — oval window. Bar — 40 μm (pertains to all parts, A-C). A) Nonimmune serum control. Epithelial tissue of utricle (U) and surrounding mesenchymal matrix were not stained. B) LC antibody is located over lateral epithelium of forming saccule (S) and U. C) CC antibody. Matrix label is not intense (4+) over forming PL and is especially dense in area in which OW is forming opposite S.

lesser extent (data not shown). Moreover, comparable modulation of S-GAG accumulation occurred in periotic mesenchyme that was cultured in the presence of otic epithelium[5] (Fig 7).

DISCUSSION

Interactions between the otocyst and its associated periotic mesenchyme are proposed to be causally related to the morphogenesis of the capsule of the mammalian inner ear.[16] We have recently shown that epithelium from the otocyst can either initiate or inhibit chondrogenesis within targeted populations of periotic mesenchymal cells.[5] In the present study, we provide evidence for TGF-β1 as a factor involved in this chondrogenic control during otic capsule formation.

Our results show that TGF-β1 polypeptide is expressed at developmental stages correlating with ongoing epithelial-mesenchymal interactions. Localization of TGF-β1 in the epithelium of the developing otocyst at 10 gd, the period just prior to the aggregation of surrounding mesenchyme, corresponds to initiation of chondrogenesis, while its second expression is concomitant with inhibition of this process. Both of these events are mediated by epithelial-mesenchymal interactions. Localization of TGF-β1 in the periotic mesenchymal extracellular matrix similarly correlates with sites of active

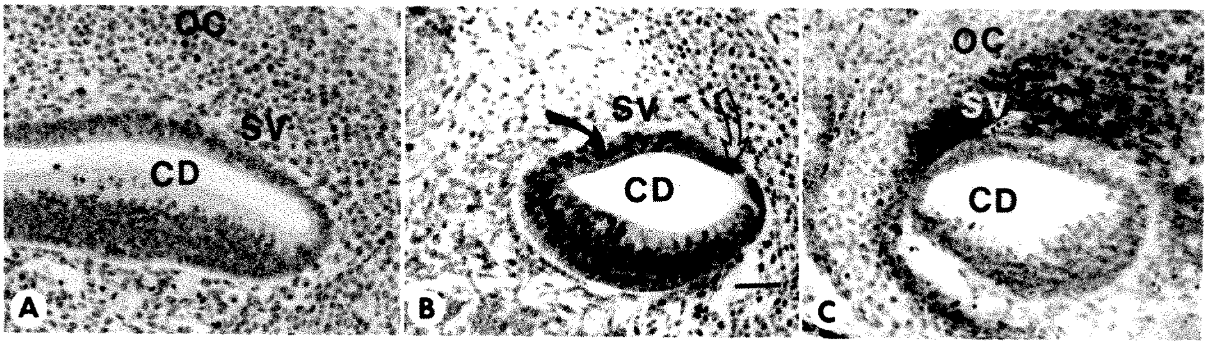

Fig 4. Specimen from mouse embryo at 14 gd, showing TGF-β1 antibodies (PAP label). Bar — 40 μm (pertains to all parts, A-C). SV — scala vestibuli, CD — cochlear duct. A) Nonimmune serum control. No immunostaining of CD epithelium was present. OC — otic capsule. B) LC antibody. Epithelium of CD does not stain uniformly. Heaviest stain (2+) is located over anlage of stria vascularis (open arrow) and Reissner's membrane (solid arrow). C) CC antibody. Immunostaining in mesenchyme surrounding cochlea is also not uniform, with no stain deposited over precartilaginous OC. Conversely, heavy stain (4+) is located over loosely organized mesenchyme of developing perilymphatic space of future SV.

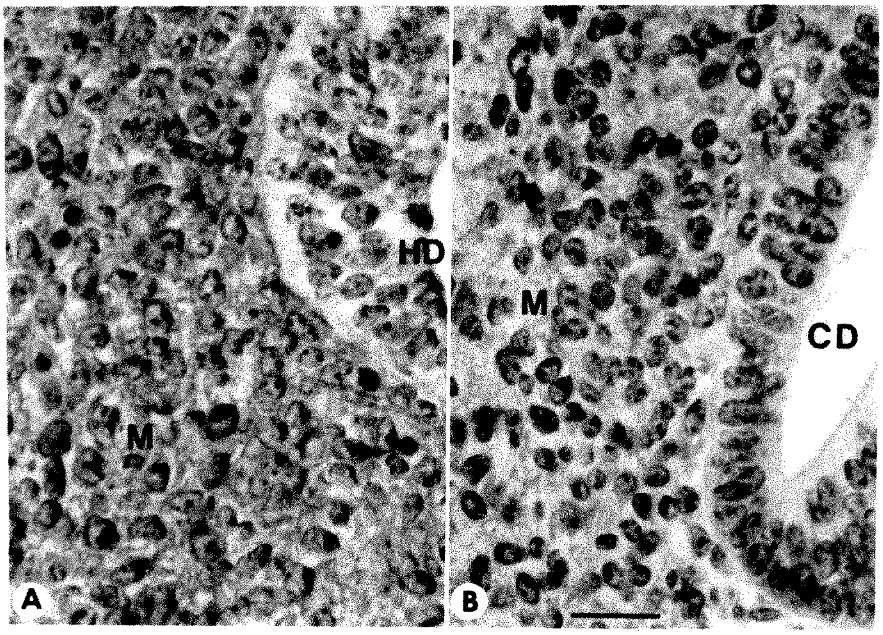

Fig 5. Specimen from mouse embryo at 12 gd, showing TGF-β1 antibodies (PAP label). Bar — 20 μm (pertains to A and B). A) Area of heaviest immunostain deposition is in mesenchyme (M) lateral to developing horizontal semicircular duct (HD). B) Area of moderate (2+) stain deposition in M lateral to developing cochlear duct (CD). Analysis of cell density shows these two areas to be approximately equivalent in cell density, whereas stain density varies considerably.

differentiation. Otic capsule formation commences with condensation of mesodermal mesenchyme in the periotic region.[17] At 12 gd, extracellular growth factor, localized within the vestibular periotic mesenchyme, is most concentrated in these sites of cellular condensation. By 14 gd, capsule chondrogenesis is complete,[17] and immunostaining of the otic capsule is no longer present. Instead, the densest immunostaining for this growth factor, now localized over the matrix in areas of loose connective tissue, correlates with sites of otic capsule sculpting and perilymphatic space formation. The specificity of TGF-β1 distribution at sites of active epithelial-mesenchymal interactions and the modulatory effects of TGF-β1 on in vitro otic chondrogenesis suggest a role for TGF-β1 in mediating these inner ear tissue interactions. Addition of TGF-β1 to high-density cultures of periotic mesenchyme either enhances chondrogenesis at 12 gd or suppresses this process at 14 gd. These actions of TGF-β1 on capsule chondrogenesis, as indicated in Fig 7, mimic the enhancement of chondrogenesis at 12 gd or the suppression of chondrogenesis at 14 gd that results when periotic mesenchyme is cultured at high den-

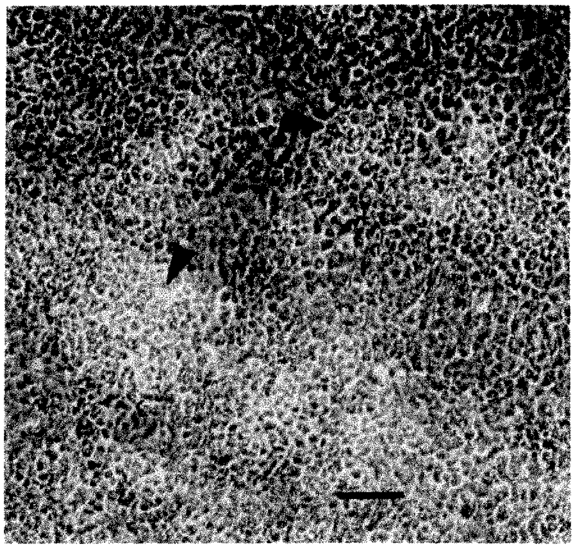

Fig 6. Twelve-gestational day periotic mesenchymal cells in high-density culture (3 days in vitro). Note sites of condensed mesenchymal cells (arrowheads). Bar — 40 μm.

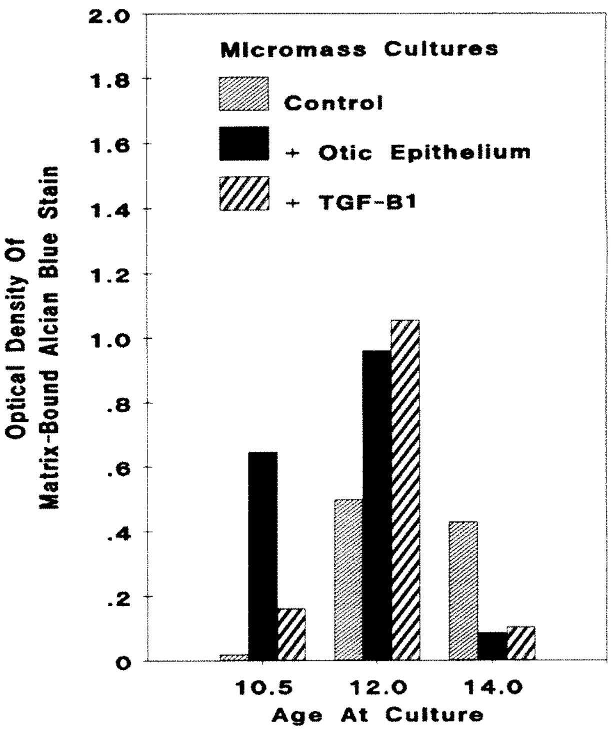

Fig 7. Histogram comparing controls to effects of otic epithelium and addition of synthetic TGF-β1 peptide (10 ng/mL; 24 hours) on accumulation of sulfated glycosaminoglycans in cultures of 10.5-, 12-, and 14-gd periotic mesenchyme. Note that addition of TGF-β1 peptide mimics effects of presence of epithelial tissue in 12- and 14-gd specimens and partially mimics epithelial effect on 10.5-gd mesenchyme cultures.

sity in the presence of otic epithelium.[5]

Of interest, at 10.5 gd TGF-β1 is localized in otic epithelium in situ, and otic epithelium can act to initiate chondrogenic differentiation in this early mesenchyme. However, the influence of TGF-β1 on 10.5-gd periotic mesenchyme results only in increased cell packing and limited S-GAG accumulation, not cartilage differentiation. In light of the modulatory effects of TGF-β1 on other growth factors, such as its potentiation of the mitogenic activity of epidermal growth factor[18] and its inhibition of the mitogenic effects of thrombin,[19] we suggest that induction of early periotic mesenchyme, similar to induction of muscle, requires the influence of more than one growth factor. It may be that TGF-β1 acts synergistically to enhance capsule chondrogenesis that at 10.5 gd is induced by another growth factor (Frenz and Van De Water, unpublished results).

The in situ distribution of this growth factor at critical morphogenetic times, taken together with its involvement in modulation of capsule chondrogenesis in vitro, suggests an important role for TGF-β1 during inner ear development. We postulate that TGF-β1, localized within the otic epithelium of the developing inner ear, acts as a paracrine regulator of the epithelial-mesenchymal tissue interactions that mediate the patterns of chondrogenesis by periotic mesenchyme during otic capsule formation. Because of its presence in the inner ear at 10.5 gd, and its apparent inability to initiate chondrogenesis in 10.5-gd periotic mesenchyme in vitro, a role as modulator rather than initiator is proposed as its mechanism of action.

ACKNOWLEDGMENT — The authors thank Rose Imperati for her technical assistance in preparation of the manuscript.

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Ann Otol Rhinol Laryngol 100:1991

FACIAL NERVE AND MEDIALLY INVASIVE PETROUS BONE CHOLESTEATOMAS

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Eight patients with extensive petrous bone cholesteatomas that invaded the labyrinth and fallopian canal are presented. The eight cases are added to a tabulation of prior literature reports to elucidate concepts of routes of extension of medially invasive temporal bone cholesteatoma. Medially invasive petrous bone cholesteatoma develops insidiously, often without symptoms other than facial palsy and/or unilateral deafness. Typically, a history of chronic ear disease can be obtained. While hearing is unlikely to be preserved in this group of patients, facial nerve function can usually be preserved, and a facial nerve graft was not necessary in our series. Acute facial nerve palsy or facial nerve paresis progressing to palsy in patients with a history of chronic ear disease should be studied radiographically for petrous bone cholesteatoma, even if there is no physical evidence of cholesteatoma.

KEY WORDS — cholesteatoma, cochlea, facial nerve, labyrinth, palsy, paresis, petrous apex, petrous bone.

INTRODUCTION

Cholesteatoma of the middle ear and mastoid remains a common indication for temporal bone operations. Typically eroded or invaded structures include the middle ear, the ossicular chain, the mastoid antrum, and the middle ear recesses such as the sinus tympani. In a study of over a thousand cholesteatoma cases, Sheehy and Brackmann[1] found the lateral semicircular canal was eroded in up to 10% of cholesteatomas. Duration of symptoms over 20 years correlated with more invasive disease. More extensive invasion of the labyrinth occurred in about 14% of the fistula cases or a little over 1% of all cholesteatoma cases. About 8% of patients experienced severe sensorineural hearing loss following operation for cholesteatoma-associated labyrinthine fistula.[1] However, when extensive erosion of the labyrinth existed, preoperative dead ears were 5 of 14 and postoperative dead ears were 10 of 14.[1]

The proximal fallopian canal and bone covering the geniculate ganglion are rarely eroded by cholesteatoma. Extensive erosion of the cochlea is, likewise, most unusual. However, the medial, anterior epitympanum anatomy appears to predispose to a specific route of medially invasive cholesteatoma growth. The route is medial to the malleus head, superior to the geniculate ganglion, and thence into the petrous bone.[2]

Of four epithelial-lined sacs that form the middle ear cleft, two predominate in the development of the anterior epitympanum. The saccus medius forms the majority of the epitympanum. The saccus medius has three secondary saccules, the anterior of which usually forms the anterior epitympanum or supratubal recess. The saccus anticus, which forms much of the middle ear, usually joins the anterior saccule of the saccus medius at the semicanal of the tensor tendon, separating the supratubal recess from the middle ear. Occasionally, the saccus anticus grows more rapidly, reaching the tegmen and the superior malleal fold.[2]

The posterior outlet of the supratubal recess is narrowed by these mucosal folds and the malleus head. Medially, the "cog," a vertical bar of bone immediately anteromedial to the malleus head and a landmark for the facial nerve, demarcates the supratubal recess.[2] Cholesteatoma coursing anterior to the malleus may fill the supratubal recess or extend along the mucosal folds into the more medial aspects of the epitympanum. Extension from this region may follow the course of the facial nerve into the medial petrous bone. In following the course of the facial nerve deep into the petrous bone, cholesteatoma may endanger the cochlea, the facial nerve, the labyrinth, and the structures of the internal auditory canal. This is the supralabyrinthine route of spread.

Similarly, cholesteatoma of the inferior middle ear may extend over the jugular bulb, through the keel of the cochlea into the jugular fossa, and along the carotid canal into the clivus. Previous reports detail extensive cholesteatoma with this type of invasion.[3,4] In this infralabyrinthine route, the otic capsule and the nerves of the jugular fossa are at risk.

A third type of petrous bone extension of cholesteatoma is translabyrinthine. Cholesteatoma may enter the labyrinth via the semicircular canals, oval window, or cochlea and progress within the labyrinth. Eventually, cholesteatoma may extend out of the otic capsule into the petrous bone.

Medially invasive petrous bone cholesteatoma is distinguished from primary petrous apex cholestea-

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Presented at the meeting of the American Otological Society, Inc, Palm Beach, Florida, April 28-29, 1990.

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COMPLICATIONS AND OUTCOMES OF MEDIALLY INVASIVE TEMPORAL BONE CHOLESTEATOMA

	This Study	*Sheehy and Brackmann*[1]	*Chu and Jackler*[2]	*Charachon*[3]	*Glasscock et al*[4]	*Yanagihara and Matsumoto*[5]	*Wright et al*[6]	*Bagger-Sjöbäck and Phelps*[7]	*Silver et al*[8]	*Totals*
Facial paresis or palsy	4	4	5	4	7	5	3	3	2	37
Conductive hearing loss	4		3	2	4	3				16
Sensory hearing loss	2		2	1	6	2				13
Mixed hearing loss	2					1	9	3		15
Disease spread route										
Supralabyrinthine	4		5	5	10			3	1	28
Intralabyrinthine	2			5					1	8
Infralabyrinthine	2			6	3					11
Petrous apex disease	2			4	3			1		10
Semicircular canal erosion	6	14		2	2			2		26
Cochlear erosion	5	5	1	2	2			3		18
Labyrinthine fallopian canal involvement	4		3	5	7	3	9	2		33
Internal canal erosion	4		3	4	7	3		3	2	26
Postoperative deafness	7	10	2	13	9		9	3		53
Postoperative facial palsy	5	4	5	8	8	6	9	3		48
Facial nerve recovery	5	3	3	7	7	1	6	2		34
Facial nerve repair				1	1	1				3
Intracranial complications				2	1		2			5
Postoperative death				2						2
Total No. of cases	8	14	5	16	15	6	9	3	4	80

toma. While some combine primary petrous apex cholesteatoma with temporal bone extension of middle ear cleft cholesteatoma,[3,4] the disorders are significantly different in behavior. As pointed out by Glasscock et al,[4] petrous apex cholesteatoma invades the internal auditory canal, then the labyrinth, producing first retrocochlear signs and symptoms. Primary petrous apex cholesteatomas appear to invade the posterior fossa commonly, whereas petrous bone extension of cholesteatoma is not inclined to do so. Experience with medially invasive petrous bone cholesteatoma is herein presented to emphasize its cranial nerve and cochleovestibular complications.

MATERIALS AND METHODS

Charts of eight patients operated on under the author's care for medially invasive temporal bone cholesteatoma were reviewed. Each case was categorized for apparent site of entrance into the petrous bone. Associated facial nerve dysfunction, hearing loss, and extent of invasion were tabulated. Complications and operative outcome were compiled.

Literature reports of similar patients were reviewed. Either tabulated information or case reports were analyzed. Whether from specific tabulated data or from detailed review of printed case reports, information similar to data compiled from the author's cases was inferred or transferred to the Table.[1-8]

CASE REPORTS

SUPRALABYRINTHINE ROUTE

Case 1. Five months prior to referral, a 30-year-old woman developed a sudden-onset right facial nerve palsy. Her facial paralysis had shown signs of recovery at about 3 months after onset. At 5 months post-onset, the face appeared to weaken again and she was referred to the author. At presentation, she had a grade 4/6 facial palsy with significant synkinesis. A remote history of right tympanoplasty operation explained a scarred tympanic membrane without apparent cholesteatoma. The audiogram revealed principally a conductive hearing loss.

Magnetic resonance imaging (MRI; Fig 1A,B) showed a large lesion involving the middle ear, supratubal recess, mastoid, labyrinth, and into the petrous bone. Computed tomography (CT; Fig 1C) demonstrated dramatic destruction of the labyrinth with erosion of the superior basal turn of the cochlea. The cholesteatoma appeared to expand the supratubal recess, as well.

The lesion was accessed via radical mastoidectomy and a translabyrinthine approach. The facial nerve was decompressed from the pyramidal bend to the internal auditory canal. Cholesteatoma covered the geniculate ganglion's superior, posterior, and inferior surfaces and extended into the vestibule. Reflection of the tympanic segment of the facial nerve anteriorly allowed removal of all cholestea-

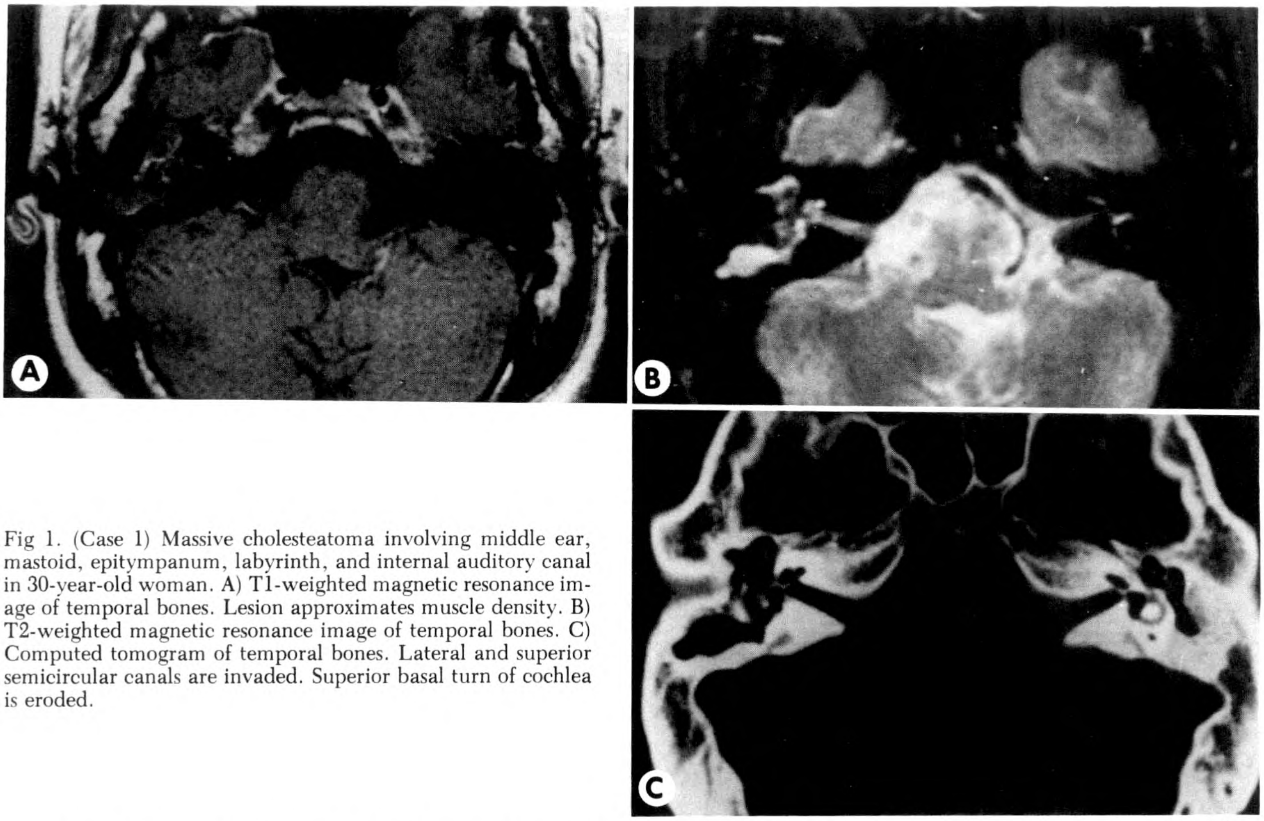

Fig 1. (Case 1) Massive cholesteatoma involving middle ear, mastoid, epitympanum, labyrinth, and internal auditory canal in 30-year-old woman. A) T1-weighted magnetic resonance image of temporal bones. Lesion approximates muscle density. B) T2-weighted magnetic resonance image of temporal bones. C) Computed tomogram of temporal bones. Lateral and superior semicircular canals are invaded. Superior basal turn of cochlea is eroded.

toma from the geniculate ganglion's posterior and inferior surfaces. Posterior reflection of the tympanic segment of the facial nerve accessed the area of cholesteatoma between the supratubal recess and the superior basal turn of the cochlea.

After the cholesteatoma was removed from the internal auditory canal, the superior vestibular nerve was found to be atrophic. The cochlear nerve and the inferior vestibular nerve appeared more normal. The facial nerve was hyperemic but intact. Facial nerve dissection was carried out with an electromyographic facial nerve monitor (Nicolet NIM II, Xomed-Treace, Jacksonville, Fla).

The resulting defect was managed with overclosure of the external auditory meatus rather than a wide open cavity because of a large cerebrospinal fluid leak. Fascia was used as a cover for the internal auditory canal. The eustachian tube was closed with bone wax. A large postauricular soft tissue flap and a temporalis muscle rotation flap obliterated the temporal bone defect.

Postoperatively, the facial nerve was no worse than preoperatively. Her facial function has improved to an approximate grade 3/6 level since operation. With the external canal closed and the temporal bone defect obliterated, long-term observation for regrowth of residual cholesteatoma is a problem. Baseline MRI scans were obtained about 3 months and 1 year postoperatively and will be repeated at annual intervals. No regrowth of disease is evident.

Case 2. A 21-year-old man was referred in February 1989 for management of a presumed medially invasive petrous bone cholesteatoma. In early 1982, at age 13, he developed meningitis and a right facial paresis in conjunction with a history of a draining ear. Following intravenous antibiotics, he underwent an intact canal wall mastoidectomy for cholesteatoma. The patient recovered from his meningitis and first operation uneventfully and had only a large conductive hearing loss as a defect. He recovered from his facial paresis.

In April 1988, meningitis and mild facial paresis recurred. Computed tomography suggested residual cholesteatoma superior to the labyrinth. His meningitis resolved with medical management, and he was referred for neurotologic management.

On initial evaluation by the author in February 1989, he was found to be neurologically intact with a thickened tympanic membrane and no obvious cholesteatoma. He had a 60-dB conductive hearing loss in the affected right ear. Computed tomography demonstrated erosion along the supralabyrinthine air cell tract. The superior basal turn of the cochlea, the superior semicircular canal, and the air cells between them extending to the internal auditory canal were involved (Fig 2).

The mastoid was explored first through an intact canal wall approach. The facial nerve was skeletonized from the stylomastoid foramen to the geniculate ganglion. Cholesteatoma was noted in the supratubal recess and over the geniculate ganglion. A

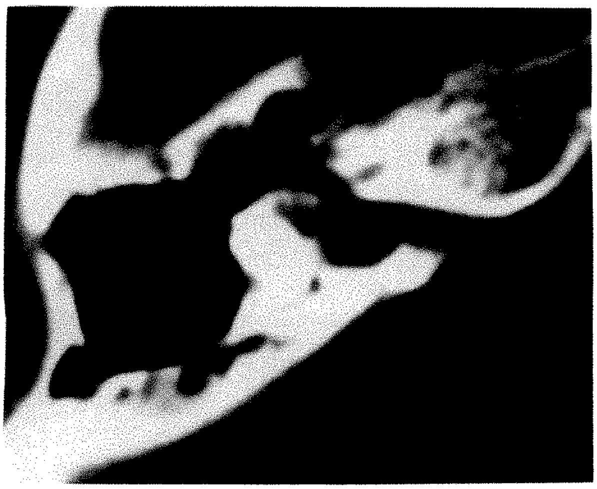

Fig 2. (Case 2) Computed tomogram of right temporal bone of 21-year-old man with prior incident of cholesteatoma-associated meningitis and facial nerve paresis. Shows residual cholesteatoma involving cochlea and labyrinth. Superior semicircular canal and superior basal turn of cochlea are eroded. Lesion overlies geniculate ganglion.

middle fossa, extradural craniotomy accessed cholesteatoma around the facial nerve and the skeletonized superior basal turn of the cochlea, which had been fenestrated by disease. Cholesteatoma dissected away from a highly thinned superior semicircular canal until a small fenestration of the canal was noted. From the small fenestration, cholesteatoma entered the superior semicircular canal and extended within the canal to both the crus communis and the vestibule. Cholesteatoma eroded the bone between the internal auditory canal and the root of the superior semicircular canal, reaching dura of the internal auditory canal and the canal for the superior vestibular nerve. A small cerebrospinal fluid leak emanated from the dural envelope of the superior vestibular nerve.

Cholesteatoma was also removed from the supratubal recess. A large piece of temporalis fascia was used to obliterate the middle fossa floor defect. The tympanic membrane was left intact and the intact canal wall mastoidectomy was closed. Facial nerve function was monitored with an electromyographic technique (Nicolet NIM II). Postoperatively, the facial nerve function remained normal. The ear healed uneventfully. The hearing was not able to be preserved.

At his first MRI session, postoperative fibrosis was identified, but no residual cholesteatoma was apparent. An annual MRI study is planned to monitor his petrous bone.

Case 3. A 60-year-old man presented with mild dizziness, hearing loss, and mild right facial paresis. He had a moderate right mixed hearing loss and his CT scan showed a lytic lesion overlying the geniculate ganglion. His mastoid was sclerotic and opacified. At intact canal wall mastoid operation, cholesterol granuloma and thickened mucosa characterized his mastoid and facial recess. The facial nerve was skeletonized from the facial recess to the geniculate ganglion. A cholesteatoma was encountered that was no more medial than the medial aspect of the geniculate ganglion. The incus and the head of the malleus were removed. Between the root of the superior semicircular canal and the superior basal turn of the cochlea, all of the cholesteatoma was able to be reached. A planned middle fossa craniotomy was not used. Facial nerve function was impaired postoperatively, but recovered to a grade 3 level. Hearing remained intact, with a conductive hearing loss postoperatively.

Case 4. A 70-year-old woman was referred with a 4- to 5-month history of progressive right facial paresis. She had a remote history of chronic ear disease, but had no prior operation. No prior history of cholesteatoma existed. Magnetic resonance imaging showed a geniculate ganglion lesion.

When first seen by the author in January 1988, she had both a marked right facial paresis, a poor grade 5/6 facial function, and synkinesis with spasm. She had normal cochlear function with bilateral conductive hearing loss. The tympanic membrane was scarred and opaque, without obvious cholesteatoma.

Computed tomography suggested erosion into the vestibule and superior basal turn of the cochlea (Fig 3). The lesion was removed via a translabyrinthine route. Hearing was not able to be preserved. Facial nerve function was unchanged immediately postoperatively and has since improved to a grade 4/6 level.

TRANSLABYRINTHINE ROUTE

Case 5. A 69-year-old man noted noise intolerance in his left ear and mild dizziness. At times, he was dizzy with exposure to loud noise. Inspection revealed a quite small attic perforation. He had a mild conductive hearing loss but fairly normal cochlear function. Computed tomography showed an extensive cholesteatoma with suspected lateral and superior canal cholesteatoma (Fig 4).

At operation, cholesteatoma was found to enter the labyrinth with a severely eroded lateral semicircular canal. Erosion extended along the lateral canal into the root of the superior semicircular canal. Cholesteatoma also filled the posterior semicircular canal and entered the vestibule. Cholesteatoma appeared to have eroded the medial convexity of the lateral semicircular canal to gain entrance to the posterior semicircular canal. The bone party wall between the facial nerve and the lumen of the lateral semicircular canal was eroded. As well, the fallopian canal was eroded away by cholesteatoma at the geniculate ganglion.

A labyrinthectomy accessed all medially invasive cholesteatoma. A radical mastoidectomy cavity was

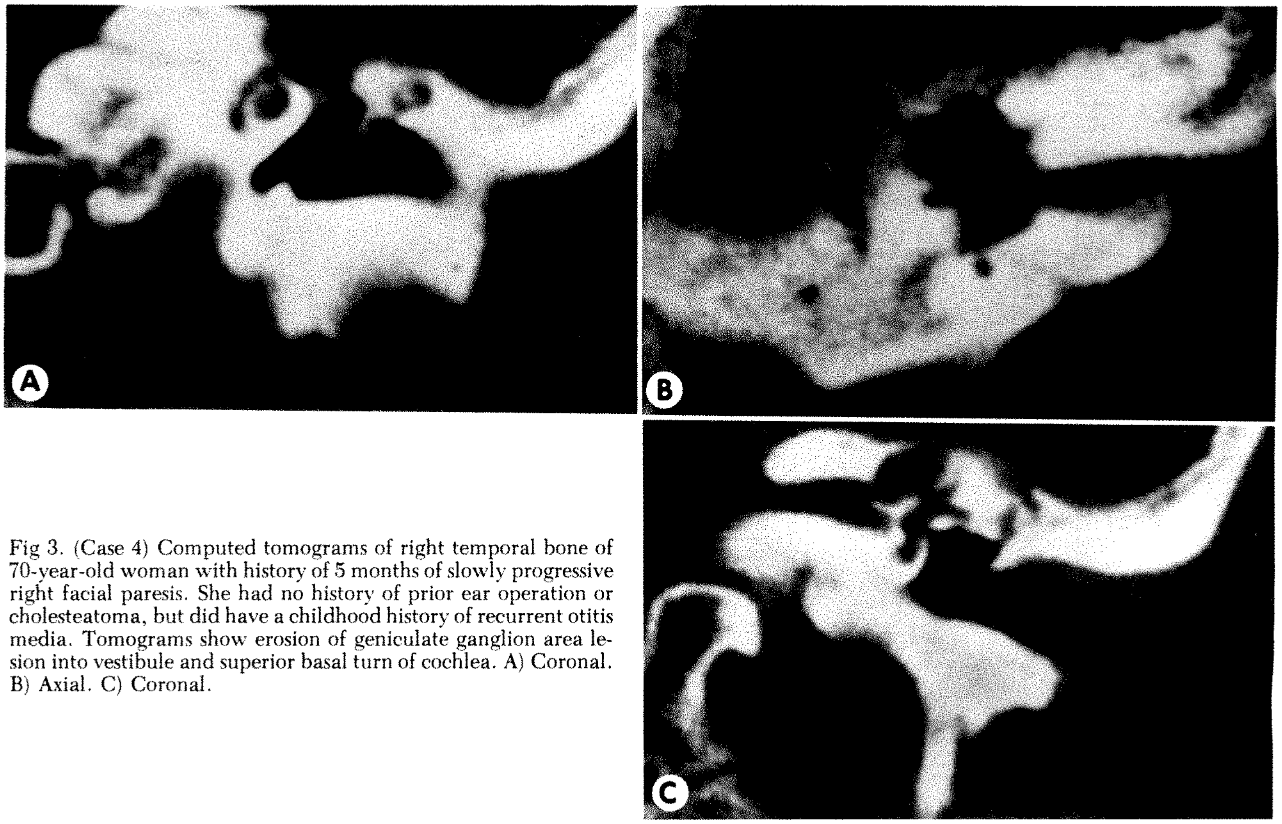

Fig 3. (Case 4) Computed tomograms of right temporal bone of 70-year-old woman with history of 5 months of slowly progressive right facial paresis. She had no history of prior ear operation or cholesteatoma, but did have a childhood history of recurrent otitis media. Tomograms show erosion of geniculate ganglion area lesion into vestibule and superior basal turn of cochlea. A) Coronal. B) Axial. C) Coronal.

created. The posterior cavity was obliterated with a soft tissue pedicle flap. Fascia was used to seal the deep cavity. Facial nerve function was monitored and was normal postoperatively. The hearing was lost. The ear has been followed up for over 2 years without evidence of residual disease.

Case 6. An 84-year-old woman was referred with a history of prior right ear operation while in her 60s. Since childhood, recurrent otorrhea had troubled the right ear. The aural meatus was stenotic and purulent debris flowed steadily from the meatus. Hearing in the left ear was consistent with her age, but she had no hearing in the right ear. Computed tomography suggested scutal absence, extensive labyrinthine erosion, and ossification of the cochlea and portions of the labyrinth.

At operation, cholesteatoma filled a previous simple mastoidectomy defect and destroyed the labyrinth. The confluence of the lateral and superior semicircular canals was filled with new bone. The posterior semicircular canal was ossified. The vestibule was filled with heavy mucous membrane. After complete labyrinthectomy, a thorough radical mastoidectomy was effected. The medial cavity was lined with fascia, the defect was obliterated with muscle and soft tissue flaps, and the aural meatus was oversewn. Facial nerve function was monitored during operation and was normal postoperatively. She recovered uneventfully.

INFRALABYRINTHINE ROUTE

Case 7. A phone call described a 20-year-old woman with a history of nine prior ear operations involving both ears. At the time of the phone call, she had been in the hospital, receiving intravenous antibiotics, for about 10 days. Admission was prompted by low-grade fever, headache, severe left earache, left shoulder paresis, and hoarseness. Computed tomography demonstrated a jugular foramen lesion.

On emergent transfer, she was found to have markedly scarred tympanic membranes bilaterally without obvious cholesteatoma. She lay curled in bed moaning with pain. She complained of severe left earache and headache. The left gag reflex was absent and left shoulder elevation was weaker than the right. Both vocal cords appeared to move, but the patient sounded mildly hoarse. High-resolution CT outlined an avascular mass in the hypotympanum and jugular fossa (Fig 5). The inferior basal turn of the cochlea was eroded, but tuning fork testing suggested a conductive hearing loss in the left ear.

The day after transfer, radical mastoidectomy with extensive removal of the floor of the tympanic ring accessed a large jugular fossa abscess and cholesteatoma. The facial nerve was skeletonized from the stylomastoid foramen to the geniculate ganglion, but was left bone-covered (in case of future need to operate on the ear). Cholesteatoma had uncovered the jugular bulb and was adherent to it. The posterior fossa dura was accessed through the retrofacial air cell tract and was lined with cholesteatoma. At the junction of the jugular bulb and sig-

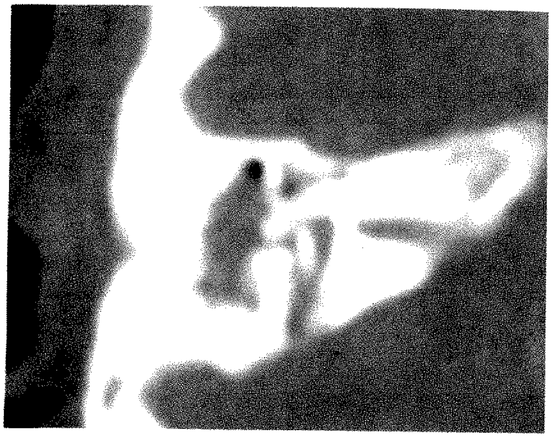

Fig 4. (Case 5) Computed tomogram of left temporal bone of 69-year-old man who had small left pars flaccida opening for large cholesteatoma. Note extensive erosion of lateral to superior semicircular canal.

moid sinus with the posterior fossa dura, removal of cholesteatoma generated a cerebrospinal fluid leak.

Anteriorly, the cholesteatoma extended along the internal carotid artery to the foramen lacerum. Cholesteatoma was meticulously peeled off all structures. Cholesteatoma fenestrated the inferior basal turn of the cochlea and hearing was lost with cholesteatoma removal. The dural defect was patched with temporalis muscle. A wide open cavity was created. The ear has been followed up for over 3 years without evidence of residual disease. In the interim, she developed a cholesteatoma in the opposite, right, only hearing ear. It has been operated on uneventfully.

Case 8. A 48-year-old man with a history of two right ear operations and five left ear operations was referred with a diagnosis of a medially invasive temporal bone mass lesion. He had been deaf in the left ear for several years. Recurrent dizziness caused him to seek medical attention. On microscopic examination of the left ear, cholesteatoma appeared to have entered the vestibule through the oval window niche. The right, opposite ear demonstrated a lateral semicircular canal fistula and a skin-covered, dehiscent tympanic segment of the facial nerve. Both ears had open mastoid cavities. Hearing was at the 25-dB level in the only hearing right ear.

An MRI study showed a medially invasive temporal bone lesion, bright on T1 and T2 imaging, consistent with cholesteatoma. The lesion appeared to extend into the internal auditory canal. A CT of the temporal bone outlined a lesion that destroyed much of the vestibular labyrinth and the inferior and medial basal turns of the cochlea and extended into the internal auditory canal, into the jugular fossa, and deeper into the temporal bone along the posterior aspect of the internal carotid artery.

At transtemporal operation, cholesteatoma was found to be extradural in the internal auditory canal, along the skull base path of cranial nerves IX, X, and XI, and adjacent to the posterior fossa dura. Cholesteatoma was adherent to the jugular dome and internal carotid artery. Cholesteatoma extension deep to the cochlea was accessed through the cochlea, creating a spinal fluid leak at the cochlear nerve entrance into the modiolus. Following apparent complete cholesteatoma removal, the bed of cholesteatoma adhesion was photocoagulated with a carbon dioxide laser. The eustachian tube was photocoagulated and obliterated with fascia. The temporal bone defect was obliterated with muscle and soft tissue rotation flaps. The aural meatus was oversewn. Postoperatively, a week of intravenous antibiotics afforded an uneventful recovery. Facial nerve function was normal.

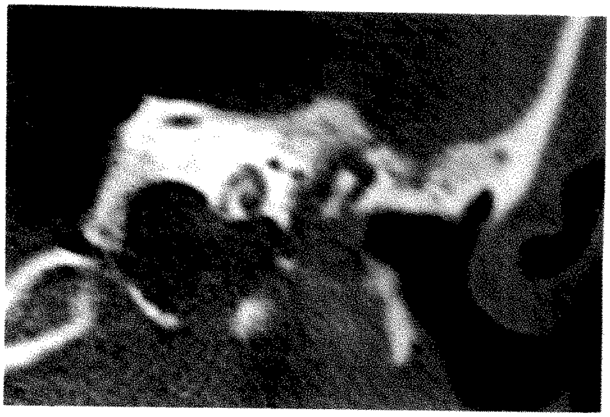

Fig 5. (Case 7) Coronal computed tomogram of left temporal bone of 20-year-old woman with multiple prior bilateral operations. Shows extensive jugular foramen lesion. Note erosion of inferior basal turn of cochlea and jugular fossa bone.

ANALYSIS OF CURRENT EXPERIENCE AND LITERATURE REVIEW

There have been a number of prior reports in the literature that deal with medially invasive petrous bone cholesteatoma. A summary of prior reports was gleaned from the references, often extrapolated by reading case histories. The Table is a compilation of data from each author reporting on medially invasive temporal bone cholesteatoma. Tabulated information was not available in many reports. Where not listed, specific information was not able to be extracted from the articles. Absence of some information may provide an inaccurately low estimation of frequency of complications of the disease.

TABULATED DATA RESULTS

Preoperative facial nerve paresis, spasm, and palsy are combined into a facial nerve dysfunction group. Note that 37 of 80 cases were so affected. In 33 of 80 cases, extension to the labyrinthine segment of the facial nerve was inferred. There were 48 recorded facial palsies postoperatively. It was often quite difficult to ascertain if operation had worsened facial nerve function, but it was clear that the facial nerve was disrupted in some of the most extensive cholesteatomas.[5] In three patients, the facial nerve was repaired: two by graft and one by direct anastomosis. Also clear is that the facial nerve was worse after operation in a significant number of patients, but that number was not able to be extracted directly from the literature. Recovery of function after operation was recorded in 34 cases. Again, improvement relative to preoperative levels of function was usually not able to be ascertained.

Significant hearing loss, as recorded, was a difficult number to extract in a specific manner from the literature, but at least 50% of patients had significant hearing loss prior to operation. Deafness after operation occurred in at least 66% — again a testimony to the aggressiveness of the disorder. Expected deafness from cochlear erosion occurred in 18. Thus, analysis of extensive petrous bone cholesteatoma discloses a high frequency of direct cochlear involvement (23%) and of inability to preserve hearing (66%). The combination of facial nerve and hearing problems seemed most common in supralabyrinthine route patients.

When route of spread to the petrous bone was recorded, the most common route was the supralabyrinthine air cell tract (see Table). A translabyrinthine or infralabyrinthine route was much less common. In the infralabyrinthine group, facial nerve problems were uncommon. In one of this author's cases, an incomplete jugular foramen syndrome was noted, but no other specific prior reports of a similar dysfunction were apparent.[3,4] Cholesteatoma extension by the infralabyrinthine route to involve the jugular bulb and internal carotid artery has been previously reported, as well, but few details were available.[3-5] In one report, infralabyrinthine extension was likely to be managed by exteriorization.[4]

Deeper erosion of cholesteatoma into the more medial petrous apex was reported or able to be inferred in about 13% of cases reviewed. Cholesteatoma extension invaded or reached the internal auditory canal in 26 (31%) of 80 cases. Similarly, intracranial complications, at 5 (6%) of 80 cases, occurred at a significant rate. A death rate of 2 (3%) comes from a single paper. A direct relationship to cholesteatoma is not apparent.

Duration of disease was not able to be extracted from the literature, in most cases, but one report[1] noted that those patients with extensive labyrinthine erosion by cholesteatoma had a 70% probability of 20 or more years with symptomatic disease.

DISCUSSION

Medially invasive petrous bone cholesteatoma should be distinguished from primary petrous apex cholesteatoma. If one perceives the petrous apex to include that part of the temporal bone deep to the superior semicircular canal, most patients reviewed do not have primary petrous apex lesions. Most medially invasive cholesteatomas involve the petrous bone: the otic capsule, internal auditory canal, and jugular fossa regions. Medially invasive temporal bone cholesteatoma is unlike primary petrous apex cholesteatoma or petrous apex cholesterol granuloma, which are primary petrous apex lesions. Medially invasive temporal bone cholesteatomas may secondarily invade the petrous apex, but most of the disease is more lateral. Such cholesteatomas are deeper than typical cholesteatomas, hence the designation "medially invasive petrous bone cholesteatoma."

Medially invasive petrous bone cholesteatoma is either a complex extension of common cholesteatoma or a primary embryonic rest. Cushing[9] first suggested that primary petrous apex cholesteatoma might arise from embryonic rests. In the series of Glasscock et al,[4] at least 3 of 15 cases reported as petrous apex cholesteatoma appeared to be primary petrous apex lesions. This report adds no new cases of extreme petrous apex congenital cholesteatoma. Two cases, though, may represent geniculate ganglion area congenital cholesteatoma.

Petrous bone, congenital cholesteatoma may explain the author's cases 3 and 5. Both lesions arose superior to and involved the geniculate ganglion without evidence of other cholesteatoma in the temporal bone. However, both ears and both patient histories evidenced prior significant trouble with chronic ear disease. Controversial is whether cholesteatoma behind an intact tympanic membrane, in the presence of chronic ear disease, can be called congenital. In a review of congenital cholesteatoma experience at the Mayo Clinic, a history of ear infection generally precluded a diagnosis of congenital cholesteatoma.[10] In their review of congenital cholesteatoma, the authors uncovered only one patient with petrous apex extension, but some of their patients appear to have developed infection secondary to cholesteatoma.[10] Thus, cholesteatoma was discovered after infection obscured the picture. It is difficult to say, unequivocally, then, that this author's two cases qualify as primary petrous bone cholesteatomas, but that is possible.

The most common route of spread of cholesteatoma to the petrous bone appears to be by the supralabyrinthine route. Four patients added to the literature by this author had supralabyrinthine disease: two possibly congenital and two by extension from the epitympanum. The latter two appear to have had cholesteatoma arising in the fashion postulated by Chu and Jackler[2]: extension from an attic cholesteatoma anterior to the malleus, filling the supratubal recess, and extending medially along the supralabyrinthine air cell tract into the petrous bone. Three reports point out that this route is probably the easiest for epitympanic cholesteatoma extension.[2,5,8] The air cell tract superior to the geniculate ganglion is surrounded by dense otic capsule bone except for relatively impenetrable dura superiorly. The bone easiest to erode is along the route of the facial nerve. The high frequency of involvement of the facial nerve and the high frequency of postoperative deafness are explained by the route of spread.

One patient studied appeared to develop intralabyrinthine cholesteatoma from an extensively eroded lateral semicircular canal fistula. Abramson et al[11] report that skin implanted in the middle ear with an adjuvant irritant can cause extensive cochlear erosion in animals. Enzymes appear to digest collagen and demineralize the bone.[11] More typical is a pushing border with a lateral semicircular canal fistula that allows matrix removal. Extensive cholesteatomatous involvement of the labyrinth has been previously reported.[1-5] In extensive erosion of the otic capsule, large areas are typically dissolved over a broad front of disease. In one case reported here, the disease instead followed the path of the lumen of the labyrinth into distant areas. Presumably, intraluminal extension occurred in the absence of an adjuvant irritant infection.

While translabyrinthine and supralabyrinthine routes of cholesteatoma are relatively common, hypotympanic spread to the petrous apex — the infralabyrinthine route — seems less commonly well described. Erosion of the semicircular canals and cochlea from lateral disease or from superior disease has been well described. Hypotympanic extension was a less common route of deep cholesteatoma invasion (11 of 80 cases reviewed). Glasscock et al[4] tended to exteriorize hypotympanic cholesteatoma rather than remove it totally. As noted by Glasscock et al, both the jugular bulb and the internal carotid artery are often exposed and covered by infralabyrinthine cholesteatoma. The posterior fossa dura may be epithelialized, too. The author's choice was complete disease removal. Spinal fluid leaks occurred in both of the author's cases, but were relatively easily managed. A laser to photocoagulate the cholesteatoma base was cautiously employed in both patients.

Clearly, the predominant problems of medially invasive petrous bone cholesteatoma are facial nerve dysfunction and deafness, often in combination. Facial nerve dysfunction may be the primary complaint and only the history of chronic ear disease may suggest the need for radiographic evaluation for cholesteatoma. From personal experience, it seems that facial nerve function can usually be preserved or improved with removal of these complex cholesteatomas. However, a role for primary facial nerve repair is apparent in patients with complete facial nerve palsy of significant duration preoperatively. When facial function does not recover at all within 6 to 9 months or when minimal function is present at a year to 15 months after operation, secondary grafting of the facial nerve seems a practical option.

While preoperative facial nerve difficulties often bring these patients to the physician, normal cochlear function in spite of cochlear erosion seems surprisingly common. Personal experience with extensive otic capsule erosion by cholesteatoma suggests that hearing is not able to be preserved in spite of middle fossa exposure. The similar difficulties others have had in the literature beg the question of how to handle the only hearing ear with such a cholesteatoma. Glasscock et al[12] have recently described most conservative operations with fairly simple but wide exteriorization of disease in such ears. Avoidance of violation of the perilymphatic spaces seems to be the only reliable method to preserve hearing. Clearly, a risk taken in hearing preservation is the chance for subsequent development of suppurative labyrinthitis, meningitis, or brain abscess. While preservation of hearing seems highly desirable, patient education on infection avoidance is critical. When infection does occur, expeditious physician care must be arranged.

In the literature review, a few cases of bilateral deafness were apparent. Clearly, in this era, the potential to use a cochlear implant lessens the devastation from bilateral profound deafness. Since cochlear implants can be used in ears with an accessible cochlear lumen even after labyrinthectomy, the cochlea should not be destroyed beyond what is essential for cholesteatoma.

Not tabulated consistently in the literature was the surgical route of disease extirpation and the basis for each. Clearly, the period of time over which these reports were generated spans the period of maturation of translabyrinthine, middle fossa, and infratemporal fossa approaches. In the author's view, when cochlear erosion is present (not an only hearing ear), a lateral approach seems most practical, since preservation of hearing is highly unlikely. From the lateral approach, all aspects of the facial nerve can be accessed, with the otic capsule removed when necessary.

If cholesteatoma extension is deep to the geniculate ganglion and the only parts of the otic capsule eroded are the semicircular canals, a middle fossa approach may be used. The middle fossa route may be combined with a standard lateral temporal bone approach for the middle ear cleft when disease so dictates. An attempt to preserve hearing may still be challenging with highly distorted anatomy.

When a cerebrospinal fluid leak occurs from a broad dural opening, management options become more difficult. One would wish to leave an aggressively exteriorized temporal bone cavity for most of the ears reported. However, total temporal bone obliteration seems least likely to result in postoperative complications from cerebrospinal fluid leak, once all of the cholesteatoma matrix has been removed. If one is to obliterate the temporal bone completely, aggressive removal of cholesteatoma matrix is essential. In this series, a laser was used, selectively, to photocoagulate prior areas of cholesteatoma attachment with one exception: when the facial nerve sheath was absent, the facial nerve was not photocoagulated.

Long-term observation of disease is more difficult in totally obliterated temporal bones. Computed tomography is theoretically less satisfactory for long-term observation, because its principal strength is bone imaging. Since MRI is so much more capable of distinguishing between cholesteatoma and fibrosis, it is more able to study sites of disease not visible through the external aural meatus. The MRI picture of cholesteatoma is muscle density on T1 images and brightness on T2 images, generally different from surrounding fibrosis.

CONCLUSIONS

1. Medially invasive petrous bone cholesteatoma is distinguished from more classic extreme petrous apex cholesteatoma. The author defines medially invasive petrous bone cholesteatoma as cholesteatoma that invades superior to, inferior to, and/or through the lateral aspect of the otic capsule to gain access to the deep temporal bone, medial to the geniculate ganglion. It is usually acquired cholesteatoma, but may be congenital.

2. The most common route of medially invasive petrous bone extension is via the supralabyrinthine route, directly superior to the geniculate ganglion and along the fallopian canal. Initial cholesteatoma extension anterior to the malleus may lead to early extension from the supratubal recess into the deep temporal bone.

3. The most common preoperative complication of medially invasive petrous bone cholesteatoma is facial nerve dysfunction: weakness, spasm, or paralysis. Paralysis or paresis may be sudden in onset or progressive, but is more commonly progressive. The facial nerve can usually be preserved and usually improves with removal of disease, but there is a significant incidence of permanent facial nerve paresis. Acute facial nerve palsy or facial nerve paresis progressing to palsy in patients with a history of chronic ear disease should be studied radiographically for petrous bone cholesteatoma, even if there is no physical examination evidence of cholesteatoma. In patients with an ear infection history, a combination of facial nerve dysfunction and hearing loss is suggestive of a supralabyrinthine lesion such as cholesteatoma.

4. Deafness before or after removal of the disease is very common in medially invasive petrous bone cholesteatoma.

5. One must be prepared to extend the dissection into the petrous apex in order to access medially invasive petrous bone cholesteatoma. Whether to use the middle fossa route or the translabyrinthine route, with or without a more traditional lateral temporal bone procedure, should be decided by review of imaging studies and consideration of hearing status.

6. The electromyographic facial nerve monitoring technique appears to help greatly in the difficult dissection encountered in removing cholesteatoma and free-floating bone fragments from the facial nerve. Its use is advocated for medially invasive petrous bone cholesteatoma.

7. Magnetic resonance imaging appears to be the most effective means of monitoring this group of patients for reappearance of residual disease. The MRI appearance of cholesteatoma is muscle density on T1 images and brightness on T2 images, generally different from surrounding fibrosis.

8. In the only hearing ear with extensive otic capsule erosion, wide exteriorization of disease may be preferred over complete disease removal.

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ANCILLARY INSTRUMENTS FOR THE VIDEO MICROLARYNGOSCOPE

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Two years of experience with the video microlaryngoscope has identified the need for ancillary instrumentation to take full advantage of the system's potential. The authors developed the following additions to video microlaryngoscopy: 1) a hinged mirror that may be articulated from its pistol grip handle; 2) a 4-mm 30° or 70° angled telescope for examination of subglottic areas not accessible by mirror examination; and 3) angulated laryngeal instrumentation that permits operation on previously obscured anterior anatomy. The authors also find that the video microlaryngoscope's distal view eliminates interference with visualization caused by the syringe during vocal cord injection.

KEY WORDS — instrumentation, laryngoscopy, video microlaryngoscope.

INTRODUCTION

The video microlaryngoscope, as previously reported,[1] was developed to simplify operative microlaryngeal procedures, provide an enhanced view of laryngeal anatomy, and permit greater ease of operation for the surgeon. In our 2 years of experience with this system, we have encountered occasional circumstances that required development of accessory instrumentation and procedures, which we will describe herein.

REVIEW OF MICROLARYNGOSCOPE SYSTEM

The video microlaryngoscope consists of an anterior-view laryngoscope with a telescope channel built into the side. Into this channel, which does not significantly increase the outside diameter of the laryngoscope, a 4-mm telescope is inserted and locked in place. An air or oxygen connection is provided to prevent fogging. The telescope objective is recessed 20 mm and centers on the laryngoscope's distal aperture. A miniature high-resolution television camera with a zoom lens is attached to the telescope's right-angled ocular, thus positioning the camera to the side, where it will not interfere with the introduction of instruments. The entire surgical procedure is performed from a high-resolution monitor positioned at the foot of the operating table (Fig 1).

The primary distinction between the microscopic and telescopic systems is point of view. The operating microscope, like the surgeon, is limited to a proximal view. It permits visualization only of anatomy that is unobstructed by the laryngoscope's narrowest inside diameter and ancillary instruments within the lumen. The telescope's objective lens is located distally, beyond such obstruction, and provides a wide-angle view with much greater depth of field. This allows the operator to complete manipulations without refocusing, as the object is always in focus despite various dimensions. The entire larynx can be clearly viewed in sharp detail, including the most anterior portion of revealed anatomy. The video microlaryngoscope permits a large image to be viewed from a convenient distance on a high-resolution television monitor. Removing an operating microscope facilitates bimanual instrumentation and manipulations, because the operator has free access to the opening of the spatula. Documentation can be simultaneously obtained on videotape, freeze frame, or electronic printer. The patient leaves the operating room with prints inserted into his or her chart displaying the lesion before, during, and after the procedure. This is an enormous advantage for future follow-up analysis or consultation. This is also an ideal method for teaching microlaryngeal surgery.

ANCILLARY INSTRUMENTATION

We would like to describe additional accessories that have enlarged the potential of video microlaryngeal applications.

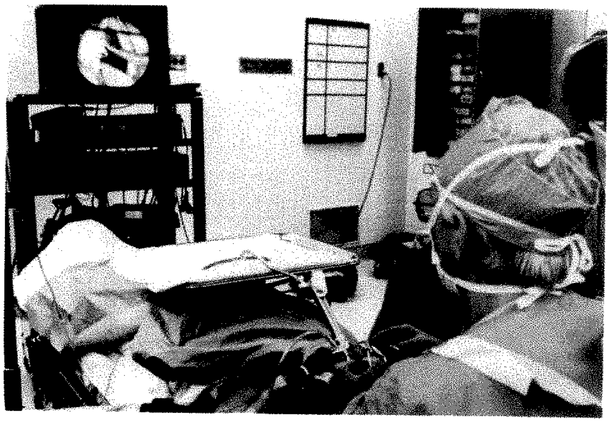

Fig 1. Surgeon operating from television monitor.

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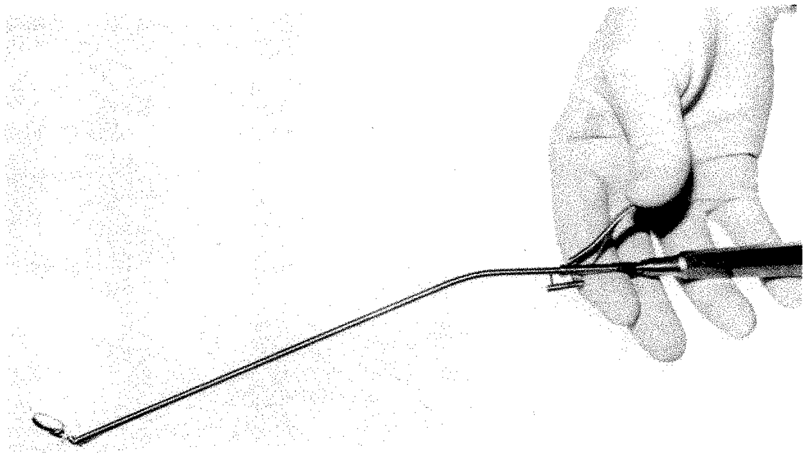

Fig 2. Observation mirror with pistol grip handle.

Folding Mirror. The video microlaryngoscope has a 6° telescope built into its wall. Therefore, it displays the vocal cords and subglottic space in a straight line. The ventricles between the false vocal cords and true vocal cords are extremely difficult, if not impossible, to visualize with a straight-forward optic, as are obscured subglottic areas and the inferior portion of the vocal cord. For this reason, we designed a small (10 mm in diameter) mirror that is attached to a pistol grip handle (Fig 2). This mechanism is attached to a hinged mirror that can be remotely angulated. The mirror is introduced through the spatula in a vertical position that facilitates passage through the cords. Once an appropriate location is obtained, the remote control mechanism on the handle enables the surgeon to angle the mirror, allowing areas not previously visualized to be seen with ease through the telescope, camera, and mirror combination. Refocusing, which would be required with the microscope, is unnecessary with the telescopic system, and previously obscured anatomy can be totally investigated in a minimum of time.

This folding mirror was used in the case of a 77-year-old woman who was evaluated for hoarseness. A magnetic resonance imaging examination showed a questionable lesion in the left ventricle and also a suspect area at the anterior portion of the left vocal cord. At the time of operation, the left ventricle was easily visualized with a mirror and completely devoid of any lesion (Fig 3A).

Another instance in which the folding mirror proved invaluable was in the case of a 45-year-old male smoker who had an obvious carcinoma of the left vocal cord at the time of operation. After a representative biopsy sample had been taken, the mirror was inserted, revealing carcinoma extending into the ventricle. Advancing the mirror between the vocal cords revealed no subglottic extension, but the tumor was seen extending just around the margin of the true cord onto its inferior surface. The use of the folding mirror quickly provided more definitive diagnosis in these two instances (Fig 3B).

Angled Telescopic System. Another approach is to observe or investigate the subglottic area via a separate 4-mm-diameter telescope that incorporates a rod-lens optic and fiberoptic light transmission. The objective lens at the working end has a fore-oblique 30° angle with a wide 60° viewing angle. There is also a 70° lateral telescope available. Both are inserted into an antifog sheath that is connected to an air pump or oxygen cylinder to avoid fogging by providing positive pressure in front of the lens. The telescope is connected to the already-present television camera, it is advanced carefully through the cords, and the areas in question are observed. Again, we would like to stress that the enlarged image is observed from a high-resolution television screen and minute lesions or changes are readily discerned. The target area is well displayed and easy access is provided together with bimanual instrumentation. This system facilitates biopsies and other manipulation and is of particular value in situations in which mirror examination is impractical.

In one patient, a 64-year-old man who had radiotherapy for glottic carcinoma, the tissue showed marked reaction to the radiotherapy, and was so edematous that it was impossible to examine the subglottic area with a mirror. Therefore, a retractor was placed in the posterior commissure and the camera was transferred from the laryngoscope to a 30° fore-oblique telescope that was inserted subglottically. The examination revealed a small, whitish patch on the left, from which a biopsy specimen was taken, revealing squamous cell carcinoma. This diagnosis was made possible through use of a subglottic telescopic examination (Fig 3C).

Special Angulated Instruments. The distal telescopic visualization permitted by the video microlaryngoscope reveals anterior anatomy that was previously obscured by the laryngoscope blade. The existing armamentarium of straight laryngeal instruments is inadequate to access these remote anatomic locations. Therefore, special microscissors and cup forceps were developed to overcome these

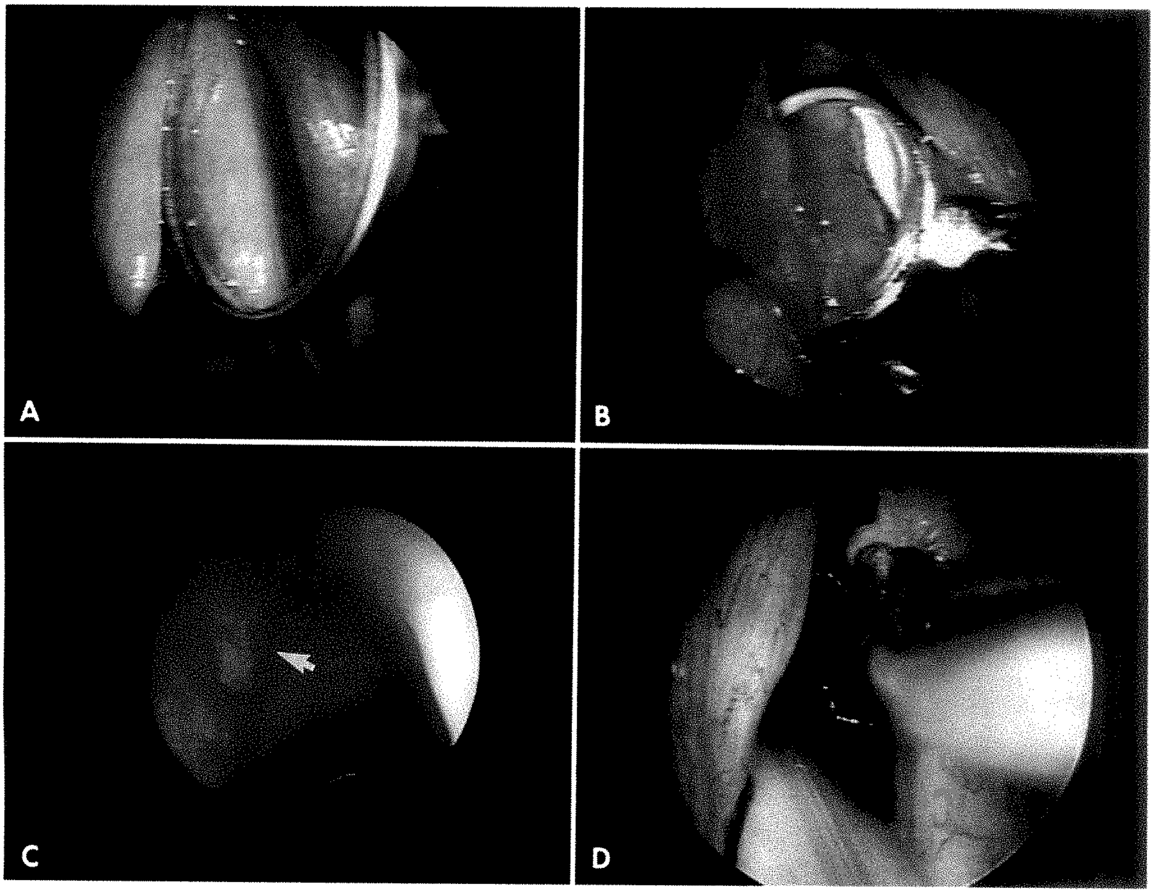

Fig 3. Patient evaluations. A) Magnetic resonance imaging had raised possibility of lesion on left ventricle, but evaluation of ventricle in mirror clearly reveals absence of any lesion. B) Mirror evaluation reveals no subglottic extension of carcinoma. C) Telescopic evaluation reveals subglottic carcinoma (arrow). D) Spindle cell carcinoma on right cord.

problems. These instruments are angulated 10° near the distal end to permit operation on difficult or inaccessible lesions. In Fig 3D we see a right vocal cord spindle cell carcinoma in a postirradiated 77-year-old man. The lesion is grasped with the angled cup forceps and excised with scissors (Fig 3D).

Injection of Vocal Cords. Owing to the telescopic optical system, more accurate placement of vocal cord–enhancing material (Teflon, Gelfoam, collagen, or fat) is facilitated. The barrel of the syringe does not obstruct the operator's view of the injection site. Only the distal shaft and needle tips are seen on the high-resolution television monitor. Our conventional injection tool can be used with more precision for inserting various materials into the cords, owing to the improved visualization and instrument access.

CONCLUSION

We feel that video microlaryngoscopy is a step forward in instrumentation for laryngeal surgery. With the addition of the above accessories, the range of its application is further increased.

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ESOPHAGEAL FOREIGN BODIES IN CHILDREN

15-YEAR REVIEW OF 484 CASES

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The findings of a retrospective analysis of the charts of 426 children admitted on 484 occasions with diagnoses of esophageal foreign bodies that were managed at the Hospital for Sick Children for 15 years to the end of 1989 are reported. In the majority of cases, ingestion of the foreign body was either witnessed or suspected. Removal was completed with the use of general anesthesia with endotracheal intubation in 90% of cases. The postcricoid area was the commonest site for impaction. Coins were the commonest foreign body. Approximately 5% of children had more than one foreign body. Fifty-nine children had esophageal anomalies. Thoracotomy or laparotomy for the retrieval of foreign bodies was necessary in less than 1% of patients. Complications occurred in 13% of patients; there were no deaths.

KEY WORDS — esophageal foreign bodies, Foley catheter extraction, medical management, rigid endoscopy.

Children often swallow foreign material or objects that will pass harmlessly through the gastrointestinal tract. Impaction will occur in the esophagus either because of the size or nature of the material ingested or because of esophageal narrowing; in such instances, removal of the impacted object or material is required. The established method for removal by most otolaryngologists is rigid endoscopy under general anesthesia. Different approaches to the management of esophageal foreign bodies (EFBs) have been advocated for some time and in fact were critically commented upon at a meeting of the American Broncho-Esophagological Association 16 years ago.[1] Recently, however, we witnessed the publication of articles not only advocating these alternative methods for the removal of EFBs — Foley catheter technique,[2-5] esophageal bougienage,[6] and flexible endoscopy[7] — but also implying that rigid endoscopy was associated with untoward morbidity and mortality.[8] With these circumstances in mind, it did seem timely to review the experience with EFBs at our institution.

PATIENT POPULATION

A retrospective review was completed of the charts of all patients admitted with the final diagnosis of EFB for the 15-year period prior to December 31, 1989. The following findings were determined at the time of chart review: year of admission, sex, age, admitting service, diagnosis on admission, whether the ingestion of the foreign body had been witnessed, history of preexisting esophageal disease, clinical symptoms on admission, type of radiographic investigation, estimated duration and site of impaction, type and outcome of management, duration of procedures under general anesthesia, status of the esophagus at the time of endoscopy, type and number of foreign body(ies) removed, occurrence of any complications, type of any open surgical procedures, and duration of hospital stay.

The information from each hospital chart was initially collected on a work sheet. Subsequently this information was entered into a VAX computer to facilitate tabulation and analysis. Where appropriate, the data have been subjected to statistical analysis.

RESULTS

During the 15-year period to the end of 1989, 426 patients (245 boys and 181 girls) between the ages of 25 days and 16 years (Fig 1) were admitted a total of 484 times with the final diagnosis of EFB. Sixty-three percent of patients were 3 years or less in age at the time of admission. Of the 56 patients under 1 year old, 8 were under the age of 6 months. On 450 occasions (93%), the patients were admitted to the otolaryngology service, with the remainder of admissions being to the general surgery service[9] and the pediatrics service.[10] The admitting diagnosis was EFB in 446 of the 484 admissions.

Fifty-nine patients (14%) had a history of esophageal anomalies requiring operation. In fact, all but 3 of the 24 patients presenting for removal of an EFB on more than one occasion belonged to this group of patients (Fig 2). There were no patients in this group of multiple removal of foreign bodies with a history of stricture formation related to caustic ingestion.

It was recorded that the ingestion of the foreign body was witnessed in 362 patients (75%). The du-

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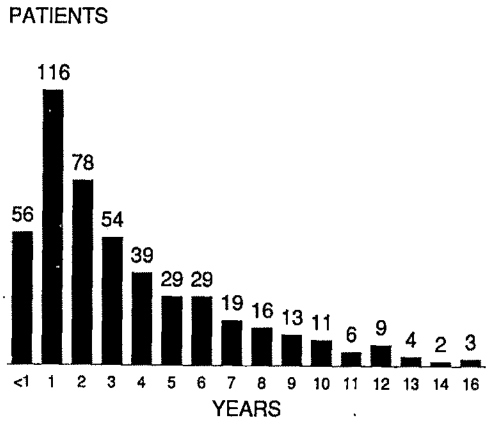

Fig 1. Age of 426 children at time of 484 admissions.

ration of impaction (Fig 3) prior to admission was less than 24 hours in 299 patients (62%), greater than 7 days in 30 patients (6%), and unknown in 48 patients (10%). The patients presented with a wide variety of signs and symptoms (Fig 4) — only 6% were recorded as being asymptomatic. Investigation consisted of an anterior-posterior chest radiographic study in 403 patients, a contrast swallow study in 48 patients, and chest fluoroscopic evaluation in 5 patients, and the findings were reported as abnormal in 329 (82%), 39 (81%), and 4 (80%), respectively.

Management consisted of observation (38 patients), medical (pharmacologic) treatment (12 patients), Foley catheter extraction (8 patients), rigid endoscopic retrieval (439 patients), and open surgical removal (4 patients).

Thirty-eight patients admitted with the diagnosis of EFB spontaneously passed the foreign body during a period of observation of 24 hours or less. These patients were differentiated from the medical group because there was no recorded effort pharmacologically to encourage passage of the foreign body. Diagnosis was made clinically or radiographically, with the type of foreign body and site of impaction determined in the same fashion. Thirty-six patients were discharged within 24 hours of admission, while the other two were discharged within the second 24 hours.

Twelve patients were treated medically with sedatives (12), analgesics (2), muscle relaxants (1), or emetics (1). In only 3 patients did the foreign body pass without further intervention. Nine patients proceeded to rigid endoscopy for foreign body removal.

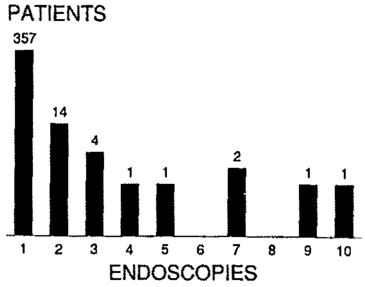

Fig 2. Number of endoscopic procedures per patient.

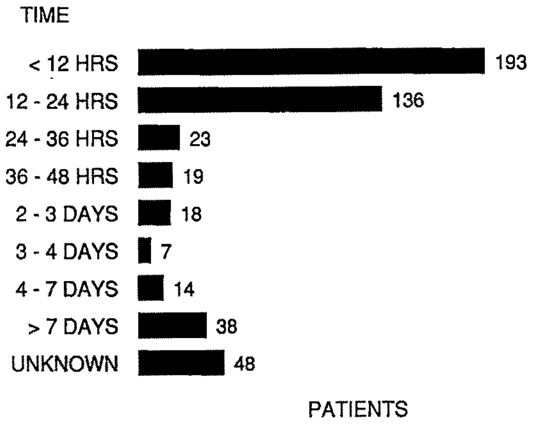

Fig 3. Duration of impaction.

A Foley catheter extraction was performed by the general surgeons in eight patients (Table 1); a foreign body was extracted in three patients only, and four patients subsequently underwent successful rigid endoscopic retrieval. It should be noted that six of these eight patients had repaired esophageal anomalies.

Open surgical removal of EFBs was necessary in four patients. Two children (1 year and 9 years of age) required thoracotomies for the removal of plastic foreign bodies that had become extraluminal. Two laparotomies were also performed. One was in an infant under 1 year of age for the removal from the stomach of an open safety pin (pushed in at the time of rigid endoscopy). The second laparotomy was in a 5-year-old child who retained a coin that would not progress out of a gastric tube previously created at the time of correction of esophageal atresia.

On 439 occasions (429 in the otolaryngology service and 10 in the general surgery service), rigid endoscopy was performed in an effort to retrieve the foreign body. Within the general surgery service, there were 6 endoscopic procedures in addition to the 4 procedures that followed unsuccessful Foley catheter extraction. In 3 of these 6 endoscopic procedures, a foreign body was retrieved; in 1 patient the foreign body was pushed into the stomach, in 1

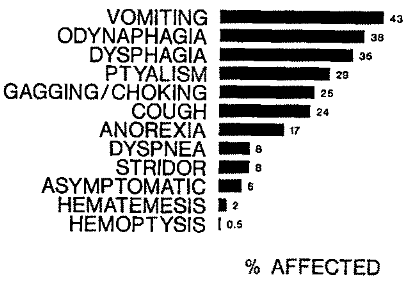

Fig 4. Clinical symptoms.

TABLE 1. FOLEY CATHETER EXPERIENCE

Age (y)	*Esophageal Anomaly*	*Esophageal Foreign Body*	*Results of Chest Radiography*	*Contrast Study*	*Foley Catheter Result*	*Rigid Endoscopy Result*
2	TEF	Food	Not done	Not done	Extraction	Not done
2	TEF	Leaf	Normal	Not done	No extraction	Not done
2	TEF	Food	Normal	Positive	No extraction	RT
3	TEF	Coin	Abnormal	Not done	No extraction	RT
4	TEF	Food	Normal	Positive	No extraction	RT
1	None	Plum pit	Abnormal	Not done	Extraction	Not done
2	None	Coin	Abnormal	Not done	Extraction	Not done
1	TEF	Plastic	Abnormal	Positive	No extraction	?

TEF — tracheoesophageal fistula, RT — retrieval, ? — outcome unknown.

it had passed spontaneously into the stomach without retrieval, and in 1 the outcome was unknown. With respect to the otolaryngology service, foreign body retrieval was attempted on 429 occasions — a foreign body was retrieved on 375 occasions, it was pushed into the stomach 15 times, it passed spontaneously without retrieval in 37 patients, and the outcome was not recorded on 2 occasions.

The nature of the foreign bodies is summarized in Fig 5; as will be appreciated, more than half (281 of 515) were coins. On 23 occasions, 2 foreign bodies were retrieved; 3 foreign bodies were retrieved 2 times. All but 3 of the 15 patients with open safety pins were under 1 year of age; these patients were recorded on 12 of 15 years of the study. The status of the esophagus was recorded as normal in 50% of the patients having endoscopy and not recorded in 94 patients (Fig 6).

The duration of the endoscopic procedure (Fig 7) was 60 minutes or less in 378 of the 420 (of the original 439 undergoing endoscopy) in whom a time had been recorded.

The duration of hospital stay (Fig 8) was 24 hours or less in 348 (72%) of the admissions. In 450 (93%) of the 484 admissions, the patients had been discharged within a 3-day period. Although coins constituted 281 (55%) of the 513 foreign bodies, only 2 of the 34 patients remaining in the hospital more than 3 days had coins as foreign bodies — these 2 children were discharged at 4 and 5 days. A review of the data of those 13 patients that remained in the hospital 8 or more days was illuminating. Five of these patients were admitted to the otolaryngology service, with 6 and 3 having been admitted to the pediatrics and the general surgery services, respectively. The foreign bodies were irregular in shape, were detected (late) in very young children, and removal was associated with complications. Six of the children in this group had strictures related to tracheoesophageal fistula repair. Two of the patients from the surgical group were in this particular group of patients.

Complications were noted on 55 (13%) occasions (Table 2) prior to, during, and following the 439 endoscopic procedures. While some of these complications caused problems (accidental extubation, etc), none were associated with any long-term morbidity. There were no deaths.

DISCUSSION

It is not surprising that there are many similarities between our series and other reports[10-12] involving a significant number of children. Boys are involved more often and the majority of patients are 2 years or less in age. Aside from a report from Hong Kong[13] in which fish bones were the commonest EFB, coins are by far the most frequently found. In most children, the ingestion of the foreign body is observed; thus, the duration of impaction is usually less than 24 hours, and management, however effected, is usually straightforward and is associated with minimal morbidity. However, it should be remembered that the presentation of an EFB impacted

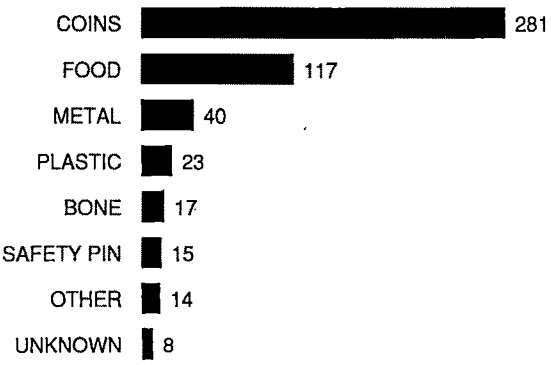

Fig 5. Foreign bodies identified radiographically or retrieved.

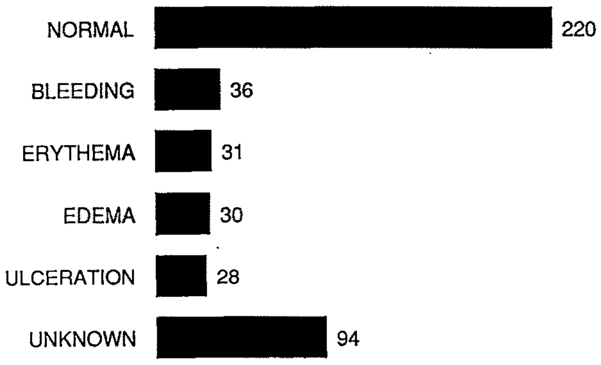

Fig 6. Status of esophagus at time of endoscopy.

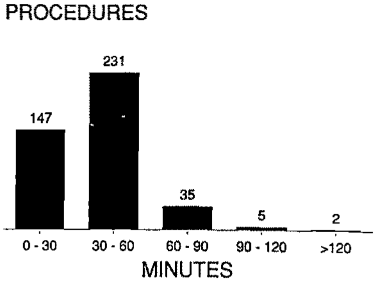

Fig 7. Duration of endoscopy as recorded in 420 of 439 procedures.

for an extended period of time may be subtle,[14-17] and such an EFB may be associated with significant morbidity and even death because of fistulization into neighboring structures.[18,19]

As we found and as has been previously reported,[10] a significant number of EFBs will move along spontaneously during a period of observation. How long should one "observe" an EFB? First of all, if the child is suspected of having ingested a disc battery (none in our series), one should treat that as an endoscopic emergency and move toward early removal, as leakage of the contents of the battery will cause tissue necrosis associated with significant morbidity.[20-22] Observation should be restricted to those children in whom the ingestion of the foreign body was observed, the foreign body has no qualities that would result in early perforation, the duration of impaction has not been greater than 24 hours, and the clinical symptoms are minimal. Although three children in our series with repaired tracheoesophageal fistulas did pass foreign bodies spontaneously, it is probably inadvisable to observe such children. Thus, we would agree that a 24-hour period of observation from the time of ingestion in such instances as outlined above is reasonable.[23]

As related, medical management was successful in only 3 of 12 patients, and really such management is rarely used by the otolaryngology staff. Such a management approach is more often advocated in the adult population,[9] and thus perhaps should be restricted to the older child who has the same criteria that make the child appropriate for observation.

Experience with the Foley catheter extraction technique in our institution has really been quite minimal, and the indifferent results may reflect poor patient selection. Although this technique has been successfully applied in children with intrinsic esophageal disease,[24] such an application of this technique is probably inappropriate.[3] It has also been suggested that this technique should not be used when the foreign body has been impacted for more than 48 hours,[5] as esophageal edema may be significant. It is suggested that if a lateral chest radiograph indicates widening (as was the case in four children in our series) of the tracheoesophageal interface (as is the case more often in children under 1½ years of age), the Foley catheter technique should not be used.[25] Experienced advocates of this technique[2-4] are concerned, as are otolaryngologists, about accidental airway obstruction and the need to observe suitable precautions. A concern expressed by the senior author[26] involves the question of informed consent, which implies that parents have been informed of risks and alternate modalities of management. Apparently the majority of radiologists performing this procedure do not obtain informed consent.[2]

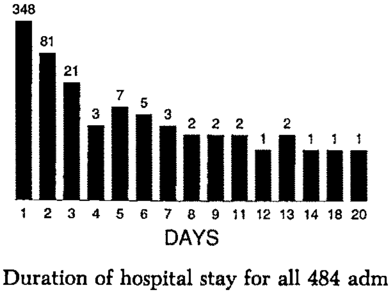

Fig 8. Duration of hospital stay for all 484 admissions.

TABLE 2. COMPLICATIONS EXPERIENCED BY PATIENTS UNDERGOING RIGID ENDOSCOPY

Prior to endoscopy	6	
Respiratory distress		3
Bradycardia		1
Seizure		1
Full stomach		1
During endoscopy	24	
Difficulty visualizing larynx		1
Arrhythmia		2
Loosened airway		2
Endotracheal tube dislodged		6
Secretions aspirated into endotracheal tube		2
Cricopharyngeal spasm		3
Laryngospasm at extubation		2
Vomiting at extubation		2
Cough at extubation		4
After endoscopy	25	
Stridor		8
Laryngospasm		3
Cough		7
Vomiting		1
Fever		3
Subglottic edema with obstruction		1
Bradycardia		1
Second endotracheal foreign body present		1

Although complications were documented in 55 patients having rigid endoscopy, none of these were associated with long-term morbidity. In fact, the complications (as pointed out by previous authors[12]) were related to the endotracheal intubation or preexisting respiratory conditions. Complications occurred in children unsuited for alternate techniques: children under 1½ years of age with foreign bodies irregular in shape that had been impacted for an extended period of time. Thus, contrary to suggestion,[8] rigid endoscopy is not associated with an untoward morbidity rate. The fact that spontaneous passage without retrieval occurred in 9% of our patients having endoscopy is disquieting; it would suggest that evaluation prior to endoscopy should be improved, as presumably a number of those procedures could have been avoided.

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NEONATAL AND PEDIATRIC MICROSUBGLOTTISCOPE SET

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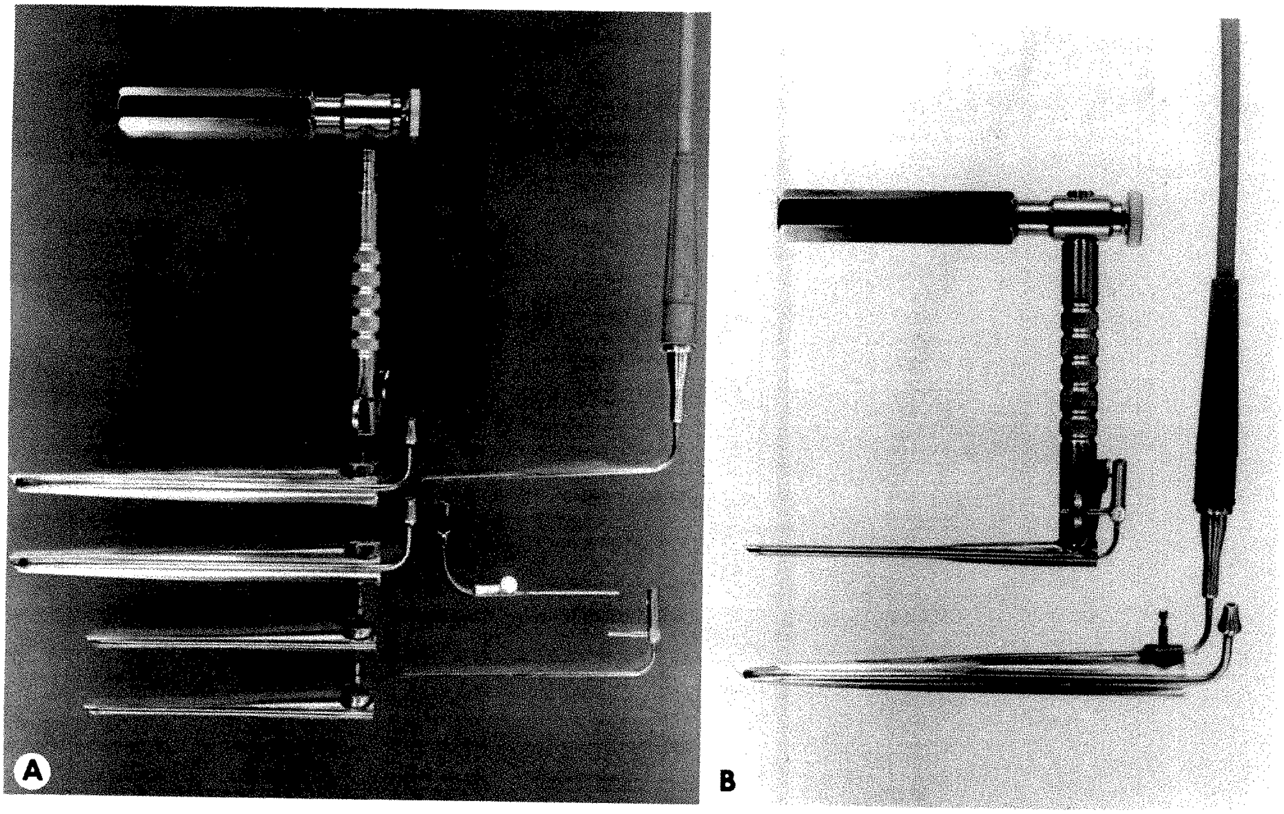
A microsubglottiscope for infants and children has been developed for microlaryngeal surgery in the glottic and subglottic regions of the larynx. The universal handle allows selection of several sizes of blades to be used according to the patient's anatomic limitations. The tips of these blades have been designed specifically to give exposure to the subglottis and upper trachea under microscopic magnification. A needle adapter for jet ventilation has been included. The authors have used this instrument in young infants and children for diagnosis and for laser resection of subglottic stenosis, hemangioma, and suprastomal granuloma, and have found the exposure to be superior to that obtained with conventional microlaryngoscopes.

KEY WORDS — laser surgery, pediatric surgery, subglottiscope.

A neonatal and pediatric microsubglottiscope set has been developed to facilitate endoscopic exposure of the subglottic larynx and upper trachea. This new microsubglottiscope uses interchangeable blades of various lengths and sizes ranging from 3 to 6 mm in tip diameter and from 12.0 to 15.7 cm in length (see Figure). This one instrument thus allows application for a wide range of patient ages and variations in anatomy. The small size of the tip allows exposure in patients with subglottic stenosis and permits one to use the operating microscope for manipulation within this area. In addition, the new laryngoscope is provided with several micro-instruments (cup forceps and scissors) that are specifically



Neonatal and pediatric microsubglottiscopes. A) Set. Universal handle will accept four different sizes of blades. Light cable has integrated light guide for larger two blades. Small venturi ventilation needle is included in set. B) Photograph demonstrating difference in size from smallest (3 mm) to largest (6 mm) blade.

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designed to work in a tiny lumen. Binocular magnification afforded by use of the microscope allows better visualization and examination than is possible with a small bronchoscope such as the 2.5 mm by 20 cm size that previously had been the only option for some of these very small patients.

The standard handle design of the laryngoscope allows suspension for microlaryngoscopy and laser work. The blades are long enough to allow its use in patients of most ages. The stainless steel tubing from which the instrument is constructed is low in specular and direct reflectance and high in diffuse and scatter reflectance, allowing relatively safe laser procedures to be performed.[1] The two larger blades use a specially manufactured light carrier, while the two smaller blades use a standard interchangeable carrier for each blade. While under suspension, the light carrier for the smallest blades can be removed and a specially designed blunt needle may be inserted down the side channel to allow for venturi jet ventilation.

This instrument has now been used in 15 patients for applications including subglottic stenosis, subglottic hemangioma, papilloma, and suprastomal granulation tissue. This particular instrument provided superior operative exposure for these regions for these particular patients when compared to a standard operating bronchoscope, laser bronchoscope, or larger pediatric subglottiscope.

In a representative case, an 11-month-old girl with prolonged intubation, status post tracheotomy, was examined for evaluation of subglottic stenosis. The subglottiscope was used with the 4-mm blade to facilitate exposure, and the Sharplan Acuspot (CO_2 Microspot) was used in an initial attempt to alleviate this patient's subglottic stenosis. She underwent two separate procedures. This patient eventually required laryngotracheoplasty at age 15 months.

PATIENT DATA

Patient	*Age*	*Diagnosis*	*Carbon Dioxide Laser*
1	3 mo	Suprastomal granulation tissue	No
2	6 mo	Suprastomal granulation tissue	No
3	7 mo	Subglottic hemangioma	Yes
4	11 mo	Subglottic stenosis	Yes
5	12 mo	Suprastomal granulation tissue	No
6	12 mo	Subglottic hemangioma	Yes
7	18 mo	Subglottic stenosis	No
8	24 mo	Subglottic stenosis	No
9	30 mo	Subglottic hemangioma	Yes
10	30 mo	Subglottic stenosis	No
11	3 y	Subglottic stenosis	Yes
12	4 y	Subglottic stenosis	No
13	4 y	Subglottic stenosis	Yes
14	7 y	Subglottic stenosis	No
15	11 y	Papilloma	Yes

The Table summarizes the authors' experience with this instrument in treating 15 patients. Potential applications for the use of the subglottiscope in the upper trachea and subglottic larynx include excision of subglottic stenosis, excision of granulomas and other benign lesions, and excision or ablation of hemangiomas and/or other obstructing subglottic lesions.[2] The unique advantage associated with the use of this subglottiscope for removing suprastomal tracheal granulomas lies in its very small size. Previous reports have described use of the Wolf bronchoscope, which has an outside diameter of 7 mm and cannot be used in very small infants.[3] Advantages of this new instrument include the capability of binocular microscopic examination during simultaneous grasping, retracting, and/or suctioning during laser resection. We have not experienced any limitations with it in exposing the operative site to date.

However, the vertical opening of these endoscopes is limited to a size to allow oral passage. This limited height necessitates the use of a carbon dioxide laser micromanipulator in which the laser beam path is coincident with the optical image. Most microslads have the mirror mounted *below* the optical path; this position would force the laser beam to hit the patient's upper lip. This limitation also existed with older styles of pediatric laryngoscopes as well. The use of a carbon dioxide micromanipulator with a coincident alignment of laser beam and optical path allows the surgeon access in very narrow apertures. The new microspots from Heraeus and Sharplan and the "hot mirror" microslad from Coherent are coincident micromanipulators. We used the Sharplan Acuspot on 7 of these 15 patients.

In conclusion, this microsubglottiscope set has been shown to be relatively safe and effective in giving surgical exposure to some very small apertures. The interchangeable blades allow for a more effective exposure for a range of patients.

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TINNITUS: THE HIDDEN EPIDEMIC

A PATIENT'S PERSPECTIVE

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The author describes his personal experience with tinnitus as well as various medical practitioners. He also discusses possible avenues for tinnitus research and suggests educational efforts that otolaryngology organizations might initiate.

KEY WORDS — hearing, tinnitus.

INTRODUCTION

One estimate is that 40 million Americans have tinnitus and that 8 million feel that the quality of their life is "significantly impaired" by it.[1] One sufferer puts it as follows: "My entire life has been disrupted and it is a daily struggle . . . There is never any peace or escape."[2] Not surprisingly, people have been known to commit suicide over it.

This sounds like a serious epidemic, about which the medical profession and the public alike would be deeply concerned. Yet many Americans have never heard of this malady. I have yet to find a school health education text that even mentions it, much less recommends preventive measures (it is probably, to a large extent, preventable). And the resources brought to bear by the medical profession, researchers and practitioners alike, seem to come up short when measured against the magnitude of the suffering that this condition entails.

ONSET OF MY TINNITUS AND MY RESPONSE TO IT

I have had tinnitus for over 2 years. During that time, I have attempted to understand why such a common and debilitating condition is treated in such a casual manner. In addition to a personal interest in this issue, I also have a professional interest: I am a psychotherapist, and I teach college courses in medical psychology.

One evening in the first week of January 1988 I noticed that I had ringing in my ears. The only unusual circumstances that I could relate to the tinnitus were that I had been relatively inactive for a few weeks with an injured back and that I had taken a single ibuprofen tablet (Advil) that morning to see if it would work better than the aspirin I had been taking. (I had never taken ibuprofen before.) The ringing was very disturbing, and after a few days I went to my family physician, who expressed sympathy and referred me to an otolaryngologist. The otolaryngologist put me through what I have since learned are the usual tests and concluded that my tinnitus, which is high-frequency, is associated with a high-frequency hearing loss due to aging (I am 52 years old), noise exposure, and/or use of certain medications. He was noncommittal on the role that ibuprofen might have played (I have since learned that this drug occasionally does cause tinnitus[3]), but had no other explanation to offer for the onset of the problem. Most disturbing of all, he said there is no effective treatment for garden-variety (idiopathic) tinnitus such as mine. This news hit me like a body blow, as I contemplated having to live indefinitely with a condition that is extremely aggravating and disruptive. I have never felt as anxious and depressed as I felt during the next several months. Many nights I did not sleep at all, and I seriously contemplated suicide for the first time in my life. Perhaps predictably, I eventually habituated to some extent to the ringing, but although I no longer think about suicide, tinnitus remains the most disrupting factor I have to deal with in my life.

MY ODYSSEY AMONG PRACTITIONERS AND OTHER RESOURCES

Altogether, I went to three otolaryngologists plus a neurologist, hoping to find some relief. Fortunately, one of the otolaryngologists mentioned the American Tinnitus Association (ATA), and I asked this organization to send information on tinnitus.

It turned out that ATA was a gold mine of information. For example, I learned from ATA, and not from any of the otolaryngologists I saw, about the wide range of things that can aggravate tinnitus. This information, in fact, was very useful, as it has helped me avoid what might have seriously aggravated my tinnitus (eg, certain antibiotics). Another thing I learned from ATA, and not from any of the otolaryngologists, is that certain treatments *are* effective in some cases of idiopathic tinnitus. After reading ATA materials and doing some literature searching of my own, I tried a number of different treatments, including the drugs Xanax (tranquilizer),[4] Lasix (diuretic),[5] and Polaramine (antihistamine).[6] My strategy is to present the relevant re-

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search to my family physician, who has been very helpful in facilitating these treatment regimens. I have also tried transcutaneous electrical stimulation,[7] a temporomandibular joint splint,[8] and (on a lark) acupuncture.[9] I have scrutinized my cholesterol, blood pressure, and diet. Of all these treatments, the only thing that seems to help is Klonopin (an anticonvulsant),[6] although I keep looking for an even more effective treatment. My point is that there is good research evidence in support of many of these treatments. Why, then, do so many otolaryngologists — if my experience is any guide — fail to even mention them to their patients? And why do they so often fail to mention preventive measures? There are at least a couple of possibilities.

One attitude I sensed on the part of the otolaryngologists I saw was something like "Oh, another tinnitus patient. Well, that's no big deal. You can learn to live with it." In other words, it's silly to spend a lot of time or effort on it. It is true that many people learn to live with tinnitus, just as many people learn to live with chronic pain (although I can say, having had chronic back pain, I would much rather have the back pain). Of course, many lay people have a similar attitude toward tinnitus — hence the remark I've heard several times: "If your ear is ringing, you'd better answer it!" However, this reaction may be a defense against underlying fears about tinnitus, as indicated by the fact that I have also had people tell me, "You mean you hear ringing, and you can't do anything to stop it? How awful!" Practitioners need to keep in mind that patients will not necessarily reveal the extent of their distress; after all, stoicism is an endemic American trait. This casual attitude toward tinnitus may have other roots as well. It is difficult to think of another common sensory disorder that is so *hidden*. Serious vision or hearing deficits are usually obvious, people in pain often favor the part of their body that hurts, etc. But unless you have tinnitus, its existence is hidden from you. It is easy to disregard.

Another attitude I sensed, which is not unique to otolaryngologists, is that the role of physicians is to 1) diagnose illness and 2) treat it, if 3) this can be done within the constraints of ordinary office or hospital visits. The physician's role does not include advice on prevention (if it involves very much time) or much time or effort spent outside the constraints of office or hospital visits (eg, conferring with specialists or researching data bases), which might be required to arrive at an effective treatment. The problem is that successfully treating a condition such as tinnitus may, because of its idiosyncratic nature, require considerable detective work beyond the scope of office visits. Certainly one culprit here is third-party providers that have established relatively narrow treatment and compensation guidelines. I have no ready solution to this dilemma, but it certainly needs to be addressed by both physicians and insurers.

THE NEED FOR IDIOSYNCRATIC MEDICINE

To illustrate the idiosyncratic nature of tinnitus and the kind of detective work it may require, let us consider my own case.

1. My tinnitus is bilateral, high-frequency (around 12,000 Hz), and narrowband.

2. The ringing usually either remains "on" throughout the course of a day or remains "off" (about equally often), although sometimes it fluctuates during the day. It is possible that these variations are triggered by either external (exogenous) conditions such as diet or internal (endogenous) conditions such as stress. However, the only connection I have been able to establish is that some noises seem to relieve it and others seem to trigger it, although neither happens dependably. For example, the sound of a shower or computer printer always eliminates the ringing for a minute or so afterward and sometimes for the rest of the day.

3. The ringing is always present upon my waking in the morning, and usually even a catnap is enough to "turn it on." (Having been asleep is necessary; just lying there awake will not produce it.) This, of course, implicates some aspect of the sleep-awake shift. The only exception to this is the following.

4. On three occasions, for a total of several days and nights, I was totally free of tinnitus. On these occasions, I was ill with viral infections, none of which seemed to involve my ears directly. The idiosyncratic nature of this response of tinnitus to illness is indicated by the fact that an ATA survey of thousands of sufferers, which included a specific question on conditions that seemed to relieve respondents' tinnitus, turned up not a single other case of relief related to illness.

In all this, it appears that there may be more than one causal mechanism involved in the appearance and disappearance of my tinnitus. But its diurnal nature (it is always "on" upon my waking in the morning) and its sensitivity to general conditions of illness implicate some systemic factor. What first comes to mind is the vascular system. But what changes occur in the vascular system during the diurnal cycle and during illness? Could any of these changes affect tinnitus? And if so, could they be relatively safely modified through treatment (possibly with drugs)?

At this point, the physicians I have seen seem stumped. Why? For one thing, knowledge concerning the vascular system is spread among various specialties, depending on what is relevant to that specialty — and only a circumscribed amount is considered relevant to otology. For another thing, much of this knowledge is considered irrelevant to any specialty and lies buried in the research literature. Hence, in cases such as this, physicians need to confer with specialists in other fields and consult the research literature. Of course, the hypothesis that conditions of the vascular system are related to my tinnitus may be incorrect. I use it, however, to point up the difficulties that medical practice faces when dealing with a condition as idiosyncratic as tinnitus. Perhaps there should be a medical journal (*The Journal of Idiosyncratic Medicine?*) in which practitioners could present puzzling cases to a wide readership on the chance that some practitioners or researchers might contribute helpful suggestions.

SOME POSSIBILITIES FOR TINNITUS RESEARCH

Let us leave the topic of patient-practitioner interaction and take a look at the larger picture of tinnitus research.

1. In the realm of basic research approaches to the treatment of tinnitus, I have been surprised that I have failed to locate adequate large-scale surveys on tinnitus. The ATA survey I mentioned previously is a good start, but ATA survey respondents were all current tinnitus sufferers. For leads on possible treatments that a few may have stumbled upon, a survey is needed of people who have had idiopathic tinnitus in the past but not currently. To what do they attribute their "cure"? Only a large-scale survey stands a chance of separating signal (promising treatments) from noise (flukes) for a question such as this. And only a large-scale survey can reveal potentially important relationships among causes, characteristics, and "cures" for a condition as idiosyncratic as tinnitus. Another obvious population to survey is physicians: clinical experience is often the first step in developing an effective treatment, and as physicians are well aware, there are very few avenues for dissemination of clinical experience.

2. In the realm of drug treatment for idiopathic tinnitus, it does not appear that government agencies and drug companies are eager to fund research to discover an effective treatment. I hope that otologists, both practitioners and researchers, are pushing them on this. An important source of leads, of course, is pharmacognosy — the subspecialty of pharmacology that studies folk use of medicinal herbs. A plant that is used in several different cultural traditions for the treatment of tinnitus might be a good one to research.

3. In the realm of potential treatments for tinnitus, one stands out in its appeal. Given that narrow-spectrum tinnitus involves very limited areas of the hearing cortex (as it is tonotopic in organization) and that removal of those areas should eliminate (conscious) awareness of tinnitus, why is brain surgery not a possible treatment in cases of intractable, incapacitating tinnitus? The answer, of course, depends on such matters as whether these cortical areas are involved in other essential brain functions, and whether the implicated areas can be reliably designated (through magnetic spectroscopy?) and then removed without inordinate risk — perhaps through focused-beam radiation ablation (gamma knife). Might similar procedures be effectively applied to the cochlea? I have yet to receive a satisfactory answer to these questions, which again may point up the insular nature of medical specialties. For example, a few neurosurgeons should have had experience with the effects of removal of areas of hearing cortex, during operations for a temporal tumor or lesion, on an occasional patient's tinnitus. But this experience will probably not find its way into the literature and in any case will not be readily available to otolaryngologists. Of course, some experimental work with these approaches to tinnitus treatment may be in progress, but if so, they are certainly not well publicized and therefore are probably not extensive.

Hence, in the arena of efforts to develop treatments for tinnitus, there are a number of promising approaches that seem to have been neglected and that might eventually yield some worthwhile treatments.

SOME SUGGESTIONS TO OTOLARYNGOLOGY PROFESSIONAL ORGANIZATIONS

I suggest that otolaryngologists, as a group of professionals, have a unique responsibility regarding tinnitus education and prevention efforts, especially considering the widespread ignorance and apathy regarding this condition. I have noticed a number of problems that otolaryngologists might be able to address, as follows.

1. Evidently, certain drugs are sufficiently ototoxic that they can cause chronic tinnitus. In my experience, warnings to this effect are seldom conveyed, either orally or in writing, to the patient. Perhaps laws in this area need strengthening.

2. It is generally accepted that loud noise can cause chronic tinnitus. However, dangerously noisy environments (eg, working conditions, rock concerts), together with the absence of hearing protectors, are still to be found. Again, more effective legislation may be needed.

3. I mentioned at the beginning of this article that I have yet to find a health education textbook that discusses tinnitus. The same holds true for most other health education materials I have seen. They generally mention hearing loss as a possible result of noise exposure, but fail to mention tinnitus, which surveys indicate is usually more debilitating than even moderate hearing loss. It is clear that health education organizations, publishers, and authors need to be "educated" about tinnitus.

More than any other group, the otolaryngology profession is in a position to facilitate needed re-forms in these areas.

SUMMARY

In many respects, tinnitus is truly a hidden condition, not only because of its very nature (it doesn't "show"), but also because of the casual attitude toward it of much of the public as well as the medical profession. This is in spite of the tremendous suffering that it entails. But attitudes can change, and if lay persons and professionals alike make the effort, perhaps we can bring tinnitus into the light of day and give it the attention it deserves.

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FUNGAL SINUSITIS IN IMMUNOCOMPROMISED CHILDREN WITH NEOPLASMS

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This paper reviews the treatment and diagnosis of immunocompromised patients with fungal sinusitis at St Jude Children's Research Hospital. Sinusitis of all types was found to be more common in patients with hematopoietic neoplasms than in patients with solid tumors; 42% of patients with leukemia had abnormal sinus radiographs. Eight cases of pathologically proven fungal sinusitis were identified. All patients were undergoing chemotherapy for either acute myeloblastic leukemia or acute lymphoblastic leukemia and had neutrophil counts less than 100 cells/mm^3. The most common findings were fever, facial pain, and abnormal sinus radiographs. Surveillance cultures of the upper aerodigestive system did not reliably predict sinus pathogens. An aggressive treatment approach consisting of early administration of amphotericin B (intravenously and via catheter irrigations of the sinuses) and surgical drainage is advocated. There was an 80% survival rate in patients in remission who were undergoing maintenance chemotherapy. All patients undergoing chemotherapy for relapse died.

KEY WORDS — children, fungal infections, leukemia, sinusitis.

INTRODUCTION

Opportunistic fungal infections commonly occur in immunosuppressed patients with neoplastic disease. These infections are most often found in patients with lymphoproliferative neoplasms, with the highest incidence in patients with acute leukemia.[1] Mirsky and Cuttner[2] found severe fungal infections at autopsy in 28% of patients who had died of acute leukemia. The most common organism was *Aspergillus* species, followed by *Candida* species. Zygomycetes (*Rhizopus* species and *Mucor* species) was found less commonly and only in conjunction with *Aspergillus* species or *Candida* species.[2] Cho and Choi[3] found fungal infections in 22% of patients who died of leukemia. Candidiasis and aspergillosis occurred with almost equal frequency, with mucormycosis (zygomycoses) occurring less frequently. Degregorio et al[4] found at least a 27% incidence of invasive fungal infection and an autopsy rate of 52% in patients treated for acute leukemia. Most of these patients had candidiasis, and the others, aspergillosis. Fifty-two (25%) of 199 children dying with leukemia at St Jude Children's Research Hospital had fungal infections at autopsy.[5]

Aspergillus species most commonly infect the lungs,[1,3,6] with involvement of the brain, heart, gastrointestinal tract, kidney, and liver also reported.[1] Pulmonary aspergillosis can be difficult to diagnose, as many patients die of the disease before treatment is initiated.[4] *Candida* species most often infects the oropharyngeal and gastrointestional tract, followed in frequency by pulmonary and disseminated disease.[3]

Localized fungal sinus involvement in pediatric immunocompromised patients is rare and few cases have been reported.[6-10] In one of the largest series, Berkow et al[6] reported five patients with aspergillosis of the paranasal sinuses, all of whom had acute lymphoblastic leukemia in relapse or neuroblastoma with bone marrow involvement; all patients died of the infection. To characterize the presentation, diagnosis, and treatment of localized fungal sinusitis, we undertook a retrospective study of patients at St Jude Children's Research Hospital.

METHODOLOGY

All sinus and nasal biopsy reports from 1970 to 1989 at St Jude Children's Research Hospital were reviewed. A total of 101 patients underwent 114 surgical procedures on the sinuses. Seventy-eight procedures (69 patients) were for diagnosis; the remaining 36 procedures (32 patients) were for the treatment of sinusitis (Table 1). A total of 7 patients with eight episodes of biopsy-proven invasive fungal sinusitis were identified. All patients had localized fungal sinusitis, although 1 patient developed

TABLE 1. MALIGNANCY AND TYPE OF SINUSITIS

	Type of Sinusitis		
Diagnosis	*Acute*	*Chronic*	*Fungal*
Acute lymphoblastic leukemia	3	16	4
Acute myeloblastic leukemia	1	1	4*
Rhabdomyosarcoma of nasopharynx		5†	
Acute lymphoblastic leukemia with lymphoma of nasopharynx		2*	

*One patient with two different episodes.

†Two patients with two different episodes.

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TABLE 2. DIAGNOSIS OF CHILDREN WITH NEOPLASMS AT ST JUDE CHILDREN'S RESEARCH HOSPITAL (1962-1989)

Neoplasm	*No. of Patients*
Solid tumors (total)	2,945
Hematopoietic tumors (total)	2,812
Acute lymphoblastic leukemia	2,140
Acute myeloblastic leukemia	574
Hodgkin's disease	447
Non-Hodgkin's lymphoma*	433
Other leukemias	84
Head and neck tumors (both solid and hematopoietic)	759
Orbit	3
Neck	32
Thyroid	5
Facial bone	15
Retinoblastoma	144
Nasopharyngeal carcinoma	37
Central nervous system	354
Other	169

*121 were head and neck tumors.

TABLE 3. YEAR IN WHICH OPERATION WAS PERFORMED

Year	*Type of Sinusitis* *Acute*	*Chronic*	*Fungal**
1970-1974		8	
1975-1979		12	
1980-1984	2	1	1
1985-1989	2	3	7

Four patients had two procedures associated with two different episodes of sinusitis.

*All cases were reported after January 1, 1984.

pulmonary involvement 10 to 19 days after the initial sinus infection.

The hospital records of the patients with sinusitis were reviewed. All cases had histologic confirmation of the infection. Histologically these fungi were identified by the following criteria. *Candida* species are characterized by pseudohyphae and yeast forms. *Aspergillus* species are characterized by septate hyphae with dichotomous branching at 45° angles. Zygomycetes is characterized by broad, aseptate, irregular hyphae with variable branching.

Presenting symptoms, associated malignancy, and treatment of both the malignancy and sinusitis were recorded.

RESULTS

All patients with sinusitis, regardless of the cause, had either leukemia or a head and neck tumor that involved the sinuses (Table 1). During this period of time, there were 2,945 patients admitted for the treatment of solid tumors and 2,812 patients admitted for the treatment of lymphoproliferative malignancies (Table 2). All of the surgical procedures for acute sinusitis occurred from 1980 on, and for fungal sinusitis, from 1984 on (Table 3). All episodes of fungal sinusitis were associated with profound granulocytopenia (neutrophil counts below 100 cells/mm^3) (Table 4). Chemotherapy was last given 3 days after to 21 days before (median, 9 days before) the onset of symptoms. The most consistent finding was facial pain, tenderness, and headache associated with fever. Patients in relapse had more intense chemotherapy than those in remission. Sinus radiographs and computed tomography scan findings were always abnormal and displayed various degrees of mucosal thickening to complete opacification of the sinuses (see Figure). In no patient were air fluid levels demonstrated. Unfortunately, the very high incidence of abnormal radiographs in patients with leukemia makes the presence of an abnormality not diagnostic of acute sinusitis. All patients were febrile at the time of symptom onset, although one temperature (case 5) was initially only 37.5°C. All patients received antibiotics. The initial treatment consisted of amikacin, vancomycin, and ticarcillin, which were usually started when the patient became febrile. Surgical intervention and si-

TABLE 4. SYMPTOMS AND THERAPY OF FUNGAL SINUSITIS PATIENTS

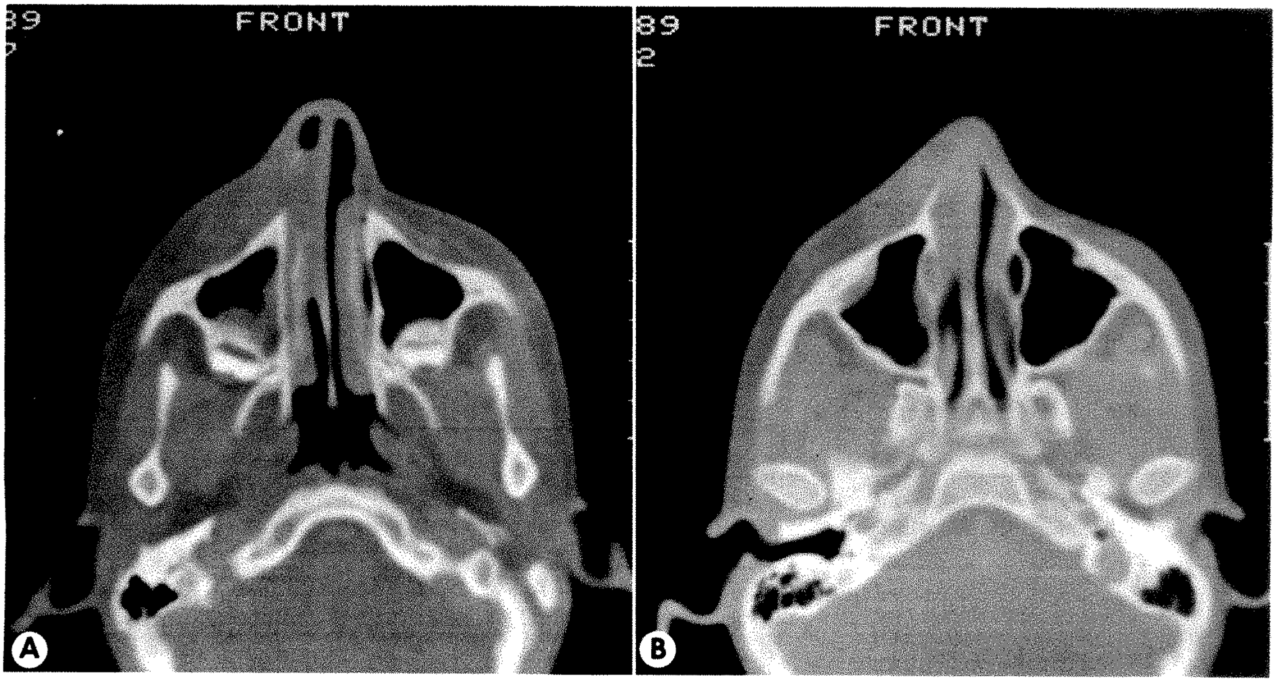
Case No.	*Symptoms*	*Fever (d)*	*Granulocytopenia <100*	*Site of Fungal Infection*	*Operations*
1	Facial pain, day 23	19	Day 10* to day 30	R maxillary	R AM, day 25
	Facial pain, day 15	5	Day 3 to day 19	L ethmoid	L ethmoidectomy, day 19
2	Headache, day 21	15	Day 20 to day 47†	R maxillary, R ethmoid	R Caldwell-Luc, L AM, Bl ethmoidectomy; day 32
3	Facial pain, drainage; day 20	9	Day 6 to day 26	R maxillary, R anterior ethmoid, R nasal turbinate	R AM, R ethmoidectomy; day 23
4	Headache, day 21; edema, day 26	19	Day 15 to day 29	L ethmoid, L sphenoid	L sphenoethmoidectomy; day 32 and day 36
5	Headache, edema; day 11	11	Day 11* to day 18	L maxillary, L anterior ethmoid	Bl AM, L catheter; day 16
6	Facial pain, edema; day 21	23	Day 13 to day 81	R maxillary, Bl ethmoid	Bl Caldwell-Luc, Bl ethmoidectomy, R catheter; day 28
7	Facial pain, edema; day 16	14	Day 12* to day 21	R maxillary, R nasal turbinate	L AM, L catheter; day 19

Day 0 taken as start of chemotherapy.

AM — large antromeatal window with maxillary sinus biopsy, Bl — bilateral.

*First recorded blood count; onset not accurately known.

†Last recorded blood count, at time of discharge to terminal care.



(Case 7) Computed tomographic scan of maxillary sinus involved with invasive aspergillosis. Only abnormality is mucosal thickening. A) Lower portion of sinus. B) Higher portion of sinus.

nus biopsy were performed 2 to 11 days after the onset of symptoms (Table 4).

The most common organism found was *Aspergillus* species. *Rhizopus* species and *Candida albicans* were found in one case each. Surveillance cultures were predictive only in one patient (Table 5), who had sinusitis due to *C albicans*. *Candida albicans* was cultured from the throat in two other patients and was not predictive of the cause of the sinusitis. Operative cultures of the sinus identified the cause of the infection in seven of eight cases (Table 5).

Treatment consisted of amphotericin B intravenously (1 mg/kg per day in all patients except patient 6, who received a dosage of 1.5 mg/kg per day), surgical drainage, and in some cases placement of an irrigation catheter. Surgical treatment was similar to that provided for a nonresponding bacterial sinusitis. All nonviable tissue was removed. However, massive operative resection of facial tissue was not needed in any patient. Amphotericin B (50 mg/L of water) irrigations (20 mL four times a day) were performed in a few patients via a red rubber catheter left in the maxillary sinus and secured to the inferior turbinate or floor of the nasal vestibule. Seven patients were thrombocytopenic (platelets less than 40,000/mm^3), with three patients having platelets less than 10,000/mm^3. All seven patients required perioperative platelet transfusions. Operative and postoperative platelet counts were kept above 45,000/mm^3 to 50,000/mm^3 for at least 7 days. Operative blood loss varied from 100 mL to 500 mL.

Early surgical and medical therapy in these patients led to a surprisingly good response (Table 6). Of the five patients in remission, only one died. This patient had the latest institution of therapy and the most malignant location of the infection (sphenoid sinus) (case 4, Table 4). Of the three patients in relapse, two were discharged home for terminal care. Their sinus infections were quiescent at the time of discharge. One patient died after 60 days with an acellular bone marrow and pulmonary aspergillosis. The sinusitis, although still active, did not spread intracranially or progress beyond the tissues adjacent to the sinus.

DISCUSSION

Although the incidence of fungal sinusitis cannot be obtained from our study, it is apparent that fungal sinusitis in immunosuppressed patients is rare and when it occurs is usually associated with leukemia[11] or a head and neck primary malignancy. Our

TABLE 5. EFFECTIVENESS OF SURVEILLANCE CULTURES

	Nose	*Nasopharynx*	*Throat*	*Blood*
Total No. of cultures	12 (4)	7 (2)	36 (8)	60 (6)
No. of positive fungal cultures predictive of fungal invasion on biopsy	—	—	2 (1)*	—
No. of positive fungal cultures not predictive of fungal invasion on biopsy	1 (1)*	—	2 (1)*	3 (1)*

Numbers in parentheses are numbers of patients, as opposed to numbers of cultures.

*All cultures positive for *Candida albicans*. One patient had candidiasis by culture but invasive aspergillosis on sinus biopsy.

TABLE 6. INFECTING ORGANISMS AND PATIENT OUTCOME IN FUNGAL SINUSITIS

Case No.	*Diagnosis*	*Organism**	*Outcome†*
1	AML in remission	*Aspergillus fumigatus*	Recovery 11 days after onset of symptoms
	AML relapse	*Aspergillus flavus*	Sinusitis quiescent, but blasts reappeared; patient discharged to terminal care 13 days after onset of symptoms; died 25 days later
2	ALL relapse	*Candida albicans*	Sinusitis quiescent; patient discharged to terminal care 25 days after onset of symptoms; died 11 days later
3	AML in remission	*Aspergillus fumigatus*	Recovery 10 days after onset of symptoms
4	AML in remission	*Aspergillus* species	Granulocytes recovered; combination of delayed treatment and surgical diagnosis, along with sphenoid location, led to fungal invasion and thrombosis of internal carotid artery
5	ALL in remission	*Aspergillus fumigatus*	Recovery 16 days after onset of symptoms
6	ALL relapse	*Rhizopus* species	Facial infection did not spread while patient received amphotericin B and catheter irrigations; developed diffuse bilateral pulmonary infiltrates on day 10 and *Rhizopus* species left lower lobe pneumonia on day 19; died on day 60 with nonrecovering bone marrow
7	ALL in remission	*Aspergillus flavus*	Recovery 13 days after onset of symptoms

ALL — acute lymphoblastic leukemia, AML — acute myeloblastic leukemia.

*All patients had localized sinus infection at time of initial diagnosis and all cases had pathologic confirmation.

†Recovery was judged as discharge date from hospital.

data also suggest that sinusitis in general (acute and chronic) is much more common in patients with leukemia or head and neck tumors than those with other solid tumors. An unpublished prospective study conducted at St Jude Children's Research Hospital from June 1970 to January 1972 found 41% of 91 patients with acute lymphoblastic leukemia had abnormal sinus radiographs at the time of induction chemotherapy. Thirty-five percent of the abnormalities consisted of minor changes but were still indicative of sinus disease. There are several possible reasons for the high incidence of sinusitis in this patient population. Although both groups of patients receive immunosuppressive chemotherapy, the patients with leukemia tend to develop a profound mucositis. Irradiation is also a factor in head and neck tumors involving the sinuses (ie, nasopharyngeal carcinoma). In five of our patients with leukemia, portions of the sinuses (frontal, sphenoid, and superior ethmoid) received approximately 24 Gy. The fact that two of our patients did not receive any cranial irradiation argues strongly against central nervous system radiotherapy as a major causative factor. Finally, it is possible that even though the leukemia is in remission, there is still a primary immunologic defect in these patients that predisposes them to the development of sinusitis. The finding that many patients with leukemia have radiographic sinus abnormalities at the time of diagnosis suggests either an immunologic defect resulting in chronic sinusitis or a structural change caused by a leukemic infiltrate.

Of the eight cases of fungal sinusitis, four occurred in patients with acute lymphoblastic leukemia and four in patients with acute myeloblastic leukemia. Since the incidence of lymphoblastic leukemia is five times greater than that of myeloblastic leukemia (Table 2), it can be concluded that fungal sinusitis is more common in acute myeloblastic leukemia (χ^2 test, $p<.05$). Other researchers have also observed the relatively high incidence of aspergillosis in patients with acute nonlymphocytic leukemia[11] and in acute myeloblastic leukemia.[2]

The occurrence of all of the cases of fungal sinusitis after 1984 is probably due to a change in the chemotherapy protocol for acute myeloblastic leukemia and acute lymphoblastic leukemia patients to one that produces more profound marrow suppression. Prolonged granulocytopenia is probably the single most important causative factor for invasive aspergillosis.[12] Other factors have included prolonged hospitalization and the administration of broad-spectrum antibiotics.[13] The clustering of three cases in the summer of 1989 (along with an associated increase in fungal infections in other sites) is possibly related to major hospital construction. Several researchers have noted that construction is associated with an increase in fungal infections in immunocompromised patients.[14,15]

A means to prevent fungal sinusitis is not known. Chronic sinusitis is common in patients with leukemia. However, the exact incidence of sinusitis warrants further investigation. At least two of our patients with fungal sinusitis had previous sinus surgery. One patient (case 1) even had two episodes of fungal sinusitis, each caused by a different species of *Aspergillus*, that presented on opposite sides and occurred 16 months apart. This patient had bilateral transantral ethmoidectomies 2 months after the first episode.

Sickles et al[16] reported that the most consistent clinical presentation of infection in profoundly granulocytopenic patients was fever, local tenderness, and erythema. The most consistent symptoms and findings in our patients with fungal sinusitis were pain (facial or headache), fever, and abnormal sinus radiographs. The abnormality on the sinus radiographs may only be mucosal thickening and may not be readily apparent on plain radiographs (see Figure). A computed tomographic examination should be considered in all patients suspected of having sinusitis. All patients were febrile at the time of symptom onset, although the temperature of one patient (case 5) was initially only 37.5°C. Facial swelling developed in 50% of the patients. These symptoms were similar to those reported by Berkow et al,[6] who reported facial pain and swelling in 55%, sinus pain in 25%, and nasal crusting or ulceration in 25% of patients.

Our experience found surveillance cultures to be unreliable, with only one of eight cases having a true positive culture. There were also two patients with a false-positive culture for *Candida* species with sinus cultures and/or pathologic study revealing aspergillosis. This is in contrast to the findings of Aisner et al,[17] who found surveillance cultures positive in 10 of 18 patients having invasive aspergillosis. However, the conclusion based upon either our data or those of Aisner et al is the same: surveillance cultures cannot rule out invasive aspergillosis. Aisner et al did find invasive aspergillosis in 10 of 11 patients with a positive culture. However, Viollier et al[13] reported positive nasal cultures for *Aspergillus* species in 19 of 21 patients with *Aspergillus* sinusitis, but also in 14 of 31 patients with non-*Aspergillus* sinusitis. (It should be noted that in Viollier's study, *Aspergillus* sinusitis was diagnosed in a subgroup of patients by the combination of positive sinus radiographs, positive anterior nasal culture, and pulmonary aspergillosis.) The relative incidence of acute fungal sinusitis to that of other causes is shown in Table 2. It is possible that the number of acute bacterial sinusitis patients is underestimated, because a few may have been empirically treated with antibiotics, improved, and did not undergo a drainage procedure. However, the vast majority of cases came to biopsy in order to rule out fungal involvement. Our results, like those of other researchers, showed that the vast majority of immunocompromised patients with fungal infection had *Aspergillus* species as the causative organism.[11] This finding may be due to the early administration of amphotericin B, since *Candida* species are much more responsive to this drug than are *Aspergillus* species.

On the basis of our experience the following treatment recommendations can be made for the profoundly immunocompromised patient.

1. In a patient with abnormal sinus radiographs, neutropenia, and facial pain, antibacterial and antifungal antibiotics should be started immediately, regardless of whether fever is present or not. Surgical biopsy and drainage should be performed as soon as the patient's hematologic status permits. (The preoperative administration of antibiotics did not preclude the culture of fungus in seven of the eight cases, and it may be unwise to operate on an infected sinus in an immunocompromised patient without preoperative administration of antibiotics.)

2. In the immunosuppressed patient with fever and abnormal sinus radiographs, antibacterial coverage is certainly indicated. The high incidence of preexisting sinus radiographic abnormalities precludes the assumption that acute sinusitis is the cause of fever in these patients. The role of empiric administration of antifungal agents is currently under study. However, the finding that 22% to 28% of patients with leukemia have fungal infections at autopsy argues strongly toward its use.

3. In the immunosuppressed patient with a fever that has not responded to 7 days of empiric antibiotics, the addition of empiric amphotericin B should be strongly considered. Stein et al[18] and Pizzo et al[19] reported a decreased incidence of fungal infections in febrile neutropenic patients who received empiric amphotericin B therapy.

4. In the immunosuppressed patient without fever or other symptoms, antibacterial and antifungal agents should not be given.

The survival rate of our patients is higher than that stated by Berkow et al[6] in a report of their own experience and review of the literature. The survival statistics of Berkow et al of only 21% were skewed by the large number of patients in relapse with nonrecovery of their bone marrow. Eighty percent (four of five) of our patients that were in remission survived. Only two of our eight patients died of fungal sinusitis. One had an aplastic bone marrow after 60 days of diagnosis and died of secondary pulmonary involvement. The other patient (case 4) had disease that was diagnosed late (positive biopsy obtained 15 days after onset of symptoms) and had a sphenoid sinusitis. A total of 13 patients could be found, including those in the literature and in our study, who developed fungal sinusitis while undergoing chemotherapy during a relapse.[6-8] None of these patients survived.

Our treatment follows the guidelines reported by Berlinger.[20] An aggressive approach needs to be taken in the treatment of these patients, with antifungal and antibacterial agents given at the time of onset of symptoms, early surgical drainage, and catheter irrigations of amphotericin B. Granulocyte transfusions, although useful in gram-negative sepsis, have not been extensively studied in fungal infections,[21] and their use in conjunction with amphotericin B has also been associated with lethal pulmonary reactions.[22] Our results are similar to those of Aisner et al,[11] who reported that all of six patients with pulmonary or sinus aspergillosis in whom the diagnosis was determined and treatment was started early had either a partial or complete response to amphotericin B therapy. The single most important factor affecting outcome is the status (remission versus relapse) of the underlying disease.[10,11]

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INTERNATIONAL HEARING AID CONFERENCE: SIGNAL PROCESSING, FITTING, & EFFICACY

The International Hearing Aid Conference: Signal Processing, Fitting, & Efficacy will be held June 21-23, 1991, at The University of Iowa, Iowa City, Iowa. The organizing committee includes Richard S. Tyler, PhD (Signal Processing), Chaslav V. Pavlovic, PhD (Fitting), and Ruth A. Bentler, PhD (Efficacy). Further information may be obtained from any member of the organizing committee at the Department of Speech Pathology and Audiology, The University of Iowa, Iowa City, IA 52242; (319) 335-8726, FAX (319) 335-8851.

Ann Otol Rhinol Laryngol 100:1991

LEIOMYOSARCOMA OF THE TRACHEA

CASE REPORT

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Leiomyosarcoma of the trachea is a rare primary tumor of the upper airway. Twelve cases have been reported in the English-language literature. Our experience with a patient with leiomysarcoma of the cervical trachea is presented. The classic symptoms, diagnosis, and surgical management of this case are contrasted with those of the previously reported cases. The surgical technique used for our patient, primary tumor resection with skin grafting and placement of a Montgomery® Laryngeal Stent, is a unique and effective treatment.

KEY WORDS — leiomyosarcoma, tracheal reconstruction, tracheal tumors.

INTRODUCTION

Leiomyosarcoma is a malignant tumor of smooth muscle. This mesenchymal tumor's occurrence in the trachea is extremely rare. The rarity of tracheal tumors often leads to a delayed clinical diagnosis, confusion regarding surgical management, and difficulty in establishing a histologic diagnosis. The following case presentation adds to 12 previously reported cases of tracheal leiomyosarcoma. A literature review along with this case report will highlight the presenting symptoms, diagnostic evaluation, and various surgical approaches and management of this tracheal tumor. A surgical technique for the resection of cervical tracheal tumors utilizing skin grafts and silicone stents will be illustrated.

CASE REPORT

A 20-year-old man presented to his general physician with a complaint of wheezing. As a tuba player, he had noted progressive difficulty in playing this instrument. A diagnosis of asthma was considered and he was treated with various bronchodilators without relief over a 2-month period. As his wheezing progressed, he was referred to a pulmonary specialist for evaluation. On routine chest radiography, a cervical tracheal mass was noted (see Figure, A). Direct laryngoscopy and bronchoscopy was performed and a large upper cervical tracheal mass encountered. This mass was partially resected. The patient's airway was much improved postoperatively. Pathologic studies provided the diagnosis of leiomyosarcoma. The patient was referred to the Massachusetts Eye and Ear Infirmary for further evaluation and management by the senior author (W.W.M.).

Upon initial presentation, the patient was mildly stridorous. Laryngeal tomograms (see Figure, B) confirmed continued narrowing of the subglottic and cervical tracheal area. Findings of the head and neck examination were normal and there was no radiographic or hematologic evidence of metastatic spread. The patient was taken to the operating room and underwent a tracheotomy and laryngofissure. The subglottic–superior cervical tracheal tumor was well visualized. The tumor along with the underlying cartilage was excised including a 0.5-cm margin of normal-appearing mucosa. A full-thickness skin graft was harvested from the right supraclavicular area and placed into the tracheal defect. A Montgomery® Laryngeal Stent (Boston Medical Products, Inc, Waltham, Mass) was placed for compression of the skin graft (see Figure, C).

The patient did well postoperatively and the laryngeal stent was removed without incident 3 weeks later. Laryngoscopy and bronchoscopy showed a 100% take of the skin graft. The patient returned to playing the tuba but over the next several months developed repeated diminished playing ability. Direct laryngoscopy and bronchoscopy revealed a significant bed of granulation tissue causing mild obstruction of the airway, which was removed with a carbon dioxide laser. Upon histologic examination, there was no evidence of persistent or recurrent malignancy.

At this time, it has been 3 years since the initial resection of this leiomyosarcoma of the trachea. There is no evidence of recurrent or metastatic disease, his airway remains excellent, and he has resumed his musical career.

PATHOLOGY

The resected subglottic tissue consisted of a pedunculated-polypoid mass with an attached base of cartilaginous fragments. Histologically, the tumor was composed of spindle cells with rounded nuclear membranes and faintly eosinophilic cytoplasm with fibrillarylike structures in some of the cells. The cellular arrangements had interlacing patterns suggestive of a smooth muscle neoplasm. In focal areas the tumor nuclei were closely packed and mitotic structures were prominent (see Figure, D). Immunohis-

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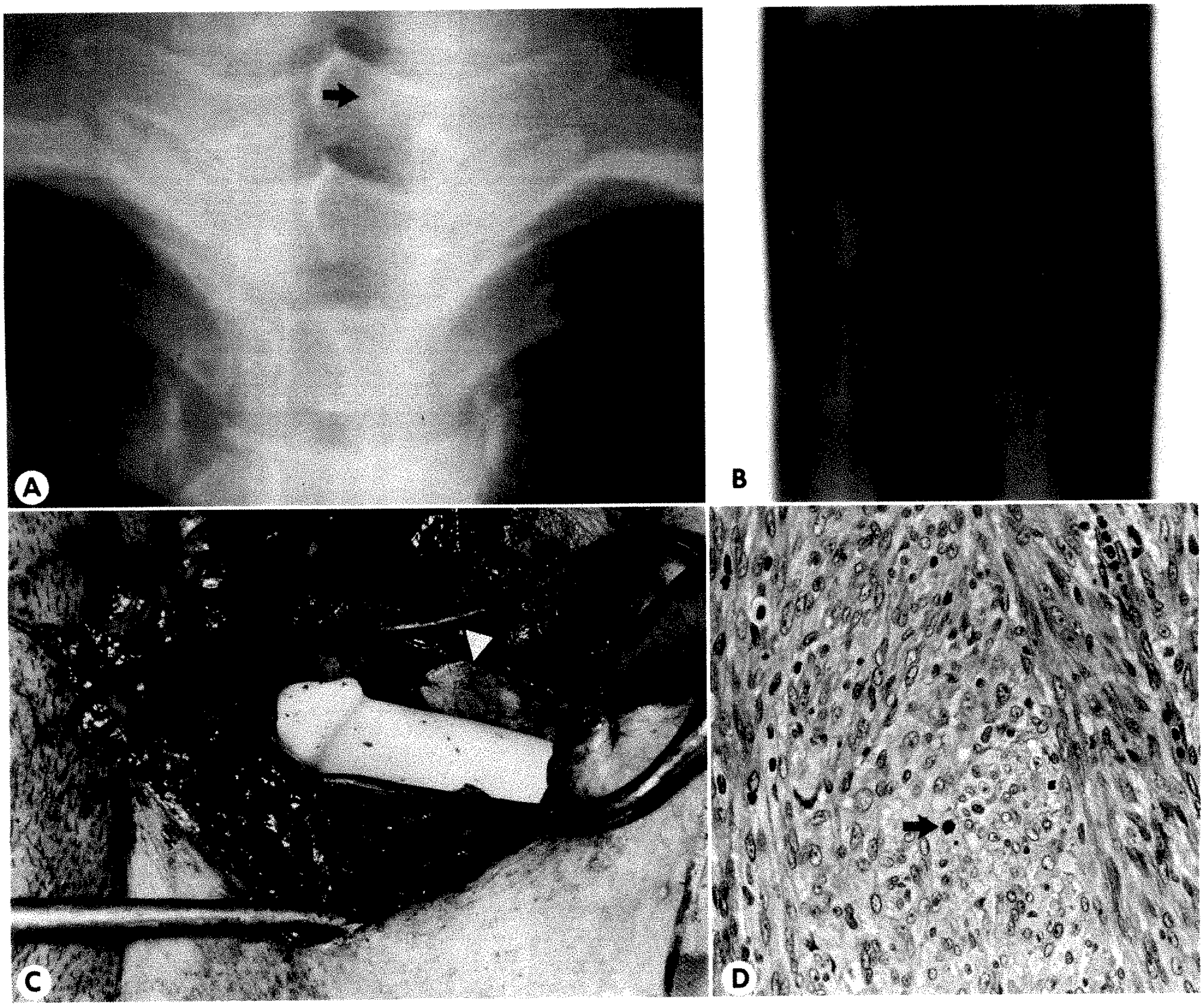

Leiomyosarcoma of trachea. A) Detail of chest radiograph. Arrow — cervical tracheal mass. B) Laryngeal tomogram demonstrating soft tissue mass (arrow) in cervical trachea. C) Montgomery® Laryngeal Stent used for compression after full-thickness skin graft (arrowhead) has been placed. D) Tumor histology. Arrow — closely packed and mitotic tumor nuclei.

tochemical stains of the tumor for myosin and desmin were negative. Electron microscopic examination of the initial biopsy specimen taken from paraffin was interpreted as showing myofibroblasts, but the preparation was suboptimal. The tumor-ring attachment to the cartilage areas was focal, with the resected margins free of tumor. The tumor morphology was interpreted as leiomyosarcoma of low-grade malignancy.

DISCUSSION

Primary tracheal tumors are unusual. Malignant tumors are more common than benign. The majority of tracheal malignancies (75% to 80%) are either squamous cell carcinoma or adenocystic carcinoma.[1-3] A recent review of 110 cases of primary malignancies of the trachea had no patients with leiomyosarcomas.[1] The incidence of primary tracheal malignancies is 1 in 1 million per year, compared to 33 in 1 million for laryngeal tumors and 348 in 1 million for lung malignancies.[4] These figures confirm that leiomyosarcoma of the trachea is an extremely rare occurrence.

A malignancy of smooth muscle, leiomyosarcoma may arise virtually anywhere in the body. Favored locations are the retroperitoneum, subcutaneous regions, omentum and mesentery, and deep structures of the extremities. Leiomyosarcomas are rare relative to leiomyomas and probably arise de novo rather than in preexisting leiomyoma. Grossly, leiomyosarcomas are usually indistinguishable from leiomyomas and show the same deceptively sharp delineation from surrounding tissue. Histologically, most agree the diagnosis and degree of aggressiveness of leiomyosarcomas are based on an increased mitotic count (>5 per 10 high-power fields), cellular atypia, necrosis, and the size of the lesion.[5]

The Table[1,3,6-10] lists the 12 previously reported cases of leiomyosarcoma of the trachea. The presenting symptoms were often dyspnea on exertion, cough, or, as in this case, considered to be asthma

SUMMARY OF 12 PREVIOUSLY REPORTED CASES OF TRACHEAL LEIOMYOSARCOMA

Authors	*Year*	*Age/Sex*	*Symptoms*	*Diagnosis*	*Location/Size*	*Operation*	*Follow-up*
Holinger et al[6]	1950	5/M	3 y, progressive dyspnea, stridor	Bronchoscopy, biopsy	2 cm below TVC, upper third of trachea, anterior wall from 2nd to 6th tracheal rings	Primary excision with delayed closure reconstruction	NED in 4½ y
Budzinski[7]	1958	33/M	Hemoptysis, "coughing of an asthmatic type"	Bronchoscopy, biopsy	4 cm below TVC, 1.0 x 1.5 cm	Primary excision	NED in 10 mo
Houston et al[1]	1969	3 cases	N/A	Bronchoscopy, biopsy	No. 1: cervical	Endoscopic removal, recurrence 6 y later, laryngectomy and partial excision of trachea	NED in 9 y
					No. 2: N/A	N/A	NED in 1 y
					No. 3: N/A	N/A	N/A
Fleetham et al[8]	1977	26/M	2 wk, cough, dyspnea, hemoptysis	Bronchoscopy	7 cm below TVC, 2 cm in diameter	Primary excision, cauterization with primary closure	N/A
Fredrickson et al[9]	1979	22/M	Cough, "asthma," dyspnea	Bronchoscopy, biopsy	4 cm below cricoid	Endoscopic removal, recurrence 6 y later, tracheal resection with staged latissimus dorsi flap	NED (time span N/A)
Pearson et al[3]	1984	4 cases	N/A	N/A	N/A	N/A	No. 1: NED in 16 mo No. 2: NED in 63 mo No. 3: NED in 125 mo No. 4: died of recurrence at 24 mo
Outzen et al[10]	1986	63/F	6 mo, dyspnea, cough, "asthma"	Bronchoscopy, biopsy	1.6 cm below TVC, 2 cm in diameter	Endoscopic removal with forceps	N/A

N/A — information not available, TVC — true vocal cords, NED — no evidence of disease.

attacks. The symptoms were present from several weeks to several years. The age at which symptoms developed ranged from 5 years to 63 years. These lesions occurred anywhere from the cricoid to the carina.

The initial diagnosis relies predominantly on radiographic evaluation. Commonly these patients have either stridor or wheezing. A chest radiograph and anteroposterior and lateral neck films often will reveal an intraluminal lesion. Tracheal tomograms will also help evaluate the extent of the lesion and whether the subglottic area is involved, along with evaluating laryngeal mobility. A computed tomographic scan of the neck and chest is useful in determining the extent of the tumor and the presence of extraluminal spread or metastatic adenopathy in the paratracheal area. Direct laryngoscopy with flexible or rigid bronchoscopy is necessary for evaluating the size of the tumor and for biopsy.

The treatment of leiomyosarcomas appears to be local resection. Experience has been obtained from the small number of previous leiomyosarcomas of the trachea and the treatment of pulmonary leiomyosarcomas.[11] As seen in the Table, surgical treatment has included endoscopic excision, open resection with primary closure, and tracheal resection with a staged reconstruction using a latissimus dorsi myocutaneous flap. Although not employed in any one of the patients presented, resection of tracheal tumors with an end-to-end anastomosis is preferred by some. The surgical approach, however, depends on the size, location, previous treatment, degree of invasion of surrounding tissues, and distant metastases.

Resection of small tumors, less than 40% to 50% of the trachea, may be accomplished without extensive delayed reconstructive efforts or a primary end-to-end anastomosis. Without extensive resection of the submucosal tissues or cartilaginous framework, the integrity of the normally rigid tubelike structure of the trachea may be preserved. These defects may be closed with a full-thickness skin graft and stented into place with either a laryngeal stent or a Montgomery® Safe-T-Tube. The laryngeal stent is used when the lesion involves the high cervical trachea of the first, second, or third cartilaginous rings. The Montgomery® Safe-T-Tube may be used to stent the skin graft in adjacent areas of the trachea.

Our patient along with nine of the patients in the Table had no evidence of recurrent disease from several months postoperatively to 12 years later. There is no comment on the survival of two additional patients. One patient died of recurrent disease approximately 2 years later.

CONCLUSIONS

1. Persistent cough, dyspnea on exertion, or asthmalike symptoms not responding to traditional medical therapy should have further evaluation to rule out a laryngeal-tracheal lesion.
2. Evaluation should include plain films, tomograms, and a computed tomographic scan along with direct laryngoscopy and bronchoscopy.
3. Surgical excision is the primary treatment for tracheal leiomyosarcomas and depends on size, location, and the extent of tumor invasion into surrounding structures.
4. A technique of primary excision with skin grafting and stenting is described.

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OBJECTIVE VOICE MEASUREMENTS & STANDARDS

A course entitled Objective Voice Measurements & Standards will be held July 22-23, 1991, at the Warwick Hotel in Philadelphia, Pennsylvania. For further information, contact The Voice Foundation, 1721 Pine Street, Philadelphia, PA 19103; (215) 735-7999.

Ann Otol Rhinol Laryngol 100:1991

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION IN CANCER OF THE HEAD AND NECK

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The syndrome of inappropriate secretion of arginine vasopressin (AVP) known as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by hyponatremia that results from water retention attributable to persistent AVP release. It may occur in a variety of malignant and nonmalignant lesions, with small cell or oat cell carcinoma of the lung by far responsible for the largest number of these cases. Cancer of the head and neck may be a rare cause of SIADH, and only a few such cases have been reported. We describe four patients with advanced cancer of the head and neck region with coexisting SIADH. Diagnosis and treatment are reported and the literature is reviewed. The possible occurrence of SIADH in the head and neck surgical practice should be kept in mind. Since SIADH is usually transient, water restriction and parenteral sodium chloride may be sufficient in overcoming the acute phase.

KEY WORDS — antidiuretic hormone, arginine vasopressin, head and neck cancer, SIADH.

INTRODUCTION

The biologically active form of antidiuretic hormone in humans is arginine vasopressin (AVP). The syndrome of inappropriate secretion of AVP known as the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is characterized by hyponatremia that results from water retention attributable to persistent AVP release. These patients are unable to excrete a dilute urine, and retention of ingested fluids occurs with expansion of the extracellular fluid volume without edema. The syndrome may arise through three pathophysiologic mechanisms: 1) discharge of AVP synthesized in tumor tissue, 2) nontumorous lung tissue's acquiring the capacity to synthesize AVP, or its reduction of left atrial filling, stimulating central AVP release, or 3) release of AVP from the neurohypophysis due to neighboring lesions or drugs, independent of normal stimuli.

Patients with SIADH may present with weight gain, lethargy, weakness, and confusion. Convulsions and coma may occur in severe cases. Low serum sodium, blood urea nitrogen, uric acid, creatinine, and albumin levels, with plasma hyposmolality and inappropriately elevated urine osmolality, are characteristic. A urinary sodium concentration of more than 20 mEq/L is suggestive of the syndrome.[1,2] To establish the diagnosis of SIADH it is essential to exclude 1) adrenal insufficiency, 2) hyponatremic edema states, 3) pseudohyponatremia associated with hyperlipidemia, 4) severe hyperglycemia, 5) hypothyroidism, 6) primary polydipsia, 7) essential hyponatremia (sick cell syndrome), and 8) renal failure.[2,3]

Since first described by Schwartz et al[4] in 1957, SIADH was reported to occur with a variety of neoplastic and nonneoplastic lesions. Occurrence of SIADH in cancer of the head and neck is rare, and only a few such cases were reported.[2,5-11] We report four patients with advanced recurrent carcinoma of the head and neck seen over a period of 10 years, with coexisting SIADH. The diagnosis and treatment are described.

The files of 260 patients suffering from carcinoma of the head and neck seen in the years 1978 to 1988 were reviewed. Four patients with recurrent metastatic cancer of the larynx and pyriform sinus were found to have suffered from SIADH during this period. The patients were all men between the ages of 40 and 65 years (mean, 58 years).

CASE REPORTS

Case 1. The patient, 62 years of age, underwent supraglottic laryngectomy and irradiation 10 years before his present admittance. He presented with T3N2M0 squamous cell carcinoma of the glottis with unilateral neck metastases and underwent total laryngectomy and neck dissection. Residual local growth was seen 3 weeks thereafter. Further treatment with cisplatin, bleomycin sulfate, and methotrexate was given. Six weeks after cessation of treatment, routine blood tests showed a sodium level of 126 mEq/L, potassium 3.1 mEq/L, urea 26 mg/dL, uric acid 2.1 mg/dL, creatinine 0.9 mg/dL, and osmolality 237 mOsm/kg. Urine osmolality was 270 mOsm/kg. Serum glucose, chloride, and albumin were normal. Serum lipid levels and thyroid function test results were normal. Chest radio-

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graphs demonstrated only mild cardiomegaly. A concurrent neurologic evaluation revealed no pathologic findings. The patient was treated by fluid restriction and a single 40-mg dose of furosemide. Increased urine levels and a return of serum and urine laboratory values to normal, except for mild hypoalbuminemia, were seen within 48 hours. No recurrence of SIADH was seen. The patient died several weeks later following rupture of the carotid artery.

Case 2. The patient, 65 years of age, underwent partial laryngectomy and unilateral neck dissection for T2N1M0 squamous cell cancer of the larynx and ipsilateral neck metastases. Three months later he presented with recurrent, poorly differentiated squamous cell tumor of the larynx with bilateral neck metastases. The patient was treated by radiotherapy and a subsequent partial chemotherapy course of cisplatin, bleomycin sulfate, and methotrexate, discontinued because of severe lymphocyte depletion. Five days later, a sudden decrease in urinary output was noted, accompanied by mild agitation. Serum sodium level was 120 mEq/L, chloride 79 mEq/L, potassium 3.1 mEq/L, and creatinine 0.8 mg/dL. Serum osmolality was 267 mOsm/kg, urine osmolality 304 mOsm/kg, and urine sodium 54 mEq/L. Serum glucose, calcium, and albumin were normal. Results of thyroid function tests and the serum lipidogram were normal. Chest radiographs were normal. The patient was initially treated with 150 mL of 5% sodium chloride, followed by an 800-mL/d fluid restriction. He responded well after the first 24 hours, with a rise in serum sodium level to 126 mEq/L and increased urinary output. The following day, however, urine output dropped to 600 mL/d, with serum sodium and chloride levels being 118 mEq/L and 84 mEq/L, respectively. The serum creatinine level was 0.9 mg/dL. Further treatment with furosemide and fluid restriction failed. The patient's condition further deteriorated and he died.

Case 3. The patient, 40 years of age, presented with bilaterally enlarged cervical lymph nodes and was found to suffer from T2N3M0 squamous cell carcinoma of the pyriform sinus. Radical neck dissection on one side and conservative neck dissection on the other side with partial pharyngectomy were done. The patient received 72 Gy postoperative irradiation, but recurrence of the tumor was seen soon thereafter. The patient received two courses of cisplatin and methotrexate without a significant effect. His condition further deteriorated. Five weeks later, routine laboratory tests showed a serum sodium level of 126 mEq/L, serum osmolality of 265 mOsm/kg, urine sodium of 104 mEq/L, and urine osmolality of 321 mOsm/kg. Creatinine clearance was 84, and serum glucose and lipid levels were normal. Thyroid and adrenal functions were within normal limits. Chest radiographs demonstrated no pulmonary disease. The patient was treated with fluid restriction and his laboratory values returned to the normal range within 36 hours, during which time he presented with no symptoms attributable to SIADH. At this stage, massive neck disease was evident with apparent compression of the remaining jugular vein. The patient died a month later with no evident recurrence of SIADH.

Case 4. The patient, 63 years of age, was hospitalized because of terminal T4N3M0 squamous cell carcinoma of the larynx. The patient had been at home and had poor compliance, but occasional laboratory test results obtained over a 2-month period demonstrated constant hyponatremia of 121 to 130 mEq/L. Serum urea and uric acid recorded once during this period were 20 mg/dL and 3.2 mg/dL, respectively. An investigation done after this period revealed a serum sodium level of 123 mEq/L, potassium 3.3 mEq/L, urea 22 mg/dL, uric acid 2.4 mg/dL, and creatinine 1.0 mg/dL. Serum osmolality was 201 mOsm/kg, urine osmolality 317 mOsm/kg, and urine sodium 23 mEq/L. Serum glucose, calcium, and albumin were normal. Results of thyroid function tests, adrenal function, and the serum lipidogram were normal. Chest radiographs and brain computed tomograms were normal. The patient evaded treatment and apparently was symptom-free apart from periods of lethargy perhaps attributable to his deteriorating general condition. Another series of tests taken a week before his death demonstrated a serum sodium level of 119 mEq/L, potassium of 4.2 mEq/L, urea of 26 mg/dL, and uric acid of 1.8 mg/dL. Serum osmolality was 181 mOsm/kg and urine osmolality 207 mOsm/kg. This documents an untreated case of chronic SIADH of over 3 months' duration. No marked symptoms were evident when the patient was seen by us, and although no form of treatment was initiated because of his near-complete lack of compliance, no severe effects were noted.

DISCUSSION

In the present series, four patients with advanced metastatic squamous cell carcinoma of the head and neck region developed hyponatremia 3 to 11 months after undergoing a surgical procedure. This hyponatremia was found by clinical and biochemical criteria to be part of SIADH. In three patients, the syndrome was transient and responded to dehydration treatment within 24 to 48 hours. The fourth patient presented with chronic SIADH that lasted for 3 months until his death and did not necessitate any treatment.

The cause for SIADH in these patients has not been established, but several pathophysiologic mechanisms may be considered.

1. Occurrence may be related to ectopic excretion of AVP or an AVP-like substance by the tumor, as was shown by Osterman et al.[6] Tumor resection re-

versed SIADH in other cases but AVP or an AVP-like substance was not detected in the tumoral tissue,[5,10] or was slightly above normal in the serum and negligible in tumoral tissue extract. It is noteworthy that Odell and Wolfson,[1] reporting on their previous experience, found elevated AVP levels in 41% of patients with carcinoma of the lung and 43% of patients with carcinoma of the colon when compared to normal subjects after 12 hours' dehydration. These patients had no clinical evidence for SIADH at that time, but presumably would manifest it if given excess water.

2. Secretion of a neurotransmitter or releasing factor for AVP by the tumor is another possibility.[12] Hayes et al[5] describe two patients with SIADH following induction chemotherapy for squamous cell carcinoma of the oropharynx and oral cavity. Although immunoperoxidase staining of the original biopsy specimens in the two patients was negative for AVP, these authors propose that a substance producing SIADH was released from the malignant cells during the rapid cytolytic phase of tumor destruction. In these two cases, SIADH was related to the administration of cisplatin and not to the existence of the tumor. Their patients developed their disorder after days 6 and 7 of their chemotherapy course. In our case 2, SIADH developed on the fifth day following termination of a partial chemotherapeutic course, and a possible connection cannot be ruled out.

3. Another mechanism was described by McQuarrie et al,[13] who have demonstrated an increased effect of AVP in patients after bilateral simultaneous neck dissection. They have experimentally shown a transient increase in the cerebral venous pressure apparently causing release of AVP and leading to renal water retention and concurrent blood volume expansion. This effect causing transient SIADH may be encountered in head and neck surgery practice and can perhaps account for the findings in patient 3, although it cannot explain our other cases or those reported in the literature.

4. Finally, invasion of the vagus nerve leading to baroreceptor denervation may lead to hyponatremia.[3]

According to the literature, SIADH is rarely encountered in the practice of head and neck surgery. A review of the literature summarized in the Table[2,5-11] revealed only 10 cases, most of which were associated with squamous cell carcinoma. The four additional cases reported herein, found over a period of 10 years, suggest that SIADH may occur more frequently than previously noted. Nevertheless, as most cases of SIADH are due to small cell and oat cell carcinomas of the lung,[1-3,7,9] a thorough examination should be done to rule out the possibility of a second neoplasm actually causing this disorder.

PATIENTS WITH SIADH ASSOCIATED WITH CANCER OF THE HEAD AND NECK

Author	*Year*	*No.*	*Tumor Location*
Moses et al[2]	1976	2	Larynx
Forrest et al[9]	1978	1	Tongue
Srigley et al[10]	1983	1	Olfactory neuroblastoma
Hayes et al[5]	1986	2	Pharynx, oral cavity
Osterman et al[6]	1986	1	Olfactory neuroblastoma
Kandylis et al[8]	1986	1	Pyriform sinus
Okutomi et al[11]	1987	1	Floor of mouth
Abdi and Bishop[7]	1988	1	Tongue
Present study	1989	4	Larynx (3), pyriform sinus (1)

Treatment of SIADH caused by excretion of AVP or an AVP-like substance requires removal or destruction of the involved tumorous tissue.[6,10] With the necessity of tumor removal notwithstanding, patients with mild to moderate symptoms should be treated primarily by fluid restriction. Intravenous administration of 3% to 5% sodium chloride and furosemide may supplement treatment. In more severe SIADH cases or prior to surgical resection, treatment with demeclocycline (600 to 1,200 mg daily) should be given. Demeclocycline, a tetracycline effective in interfering with the renal action of AVP, was found to be superior to lithium in SIADH patients.[9]

Although diagnosis can be established by the patient's symptoms, serum and urine laboratory values, and response to treatment, serum AVP levels should be recorded where possible, and tumor specimens should be evaluated by immunohistochemical staining when available. Although not always clinically evident, the possibility of occurrence of SIADH in such cases should be remembered, and early treatment initiated to prevent further morbidity in these compromised patients.

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FIRST INTERNATIONAL CONFERENCE ON ACOUSTIC NEUROMA

The First International Conference on Acoustic Neuroma will be held Aug 25-29, 1991, in Copenhagen, Denmark. For further information, contact Copenhagen Acoustic Neuroma Conference, Secretariate, ENT Department, Gentofte University Hospital, DK-2900 Hellerup, Copenhagen, Denmark.

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FIRST INTERNATIONAL SKULL BASE CONGRESS

The First International Skull Base Congress will be held June 14-20, 1992, in Hanover, Germany. For further information, contact Madjid Samii, MD, Professor and Chairman of Neurosurgery, Medical School Hanover, Neurosurgical Clinic, Hospital Nordstadt, Haltenhoffstr 41, D-3000 Hanover 1, Germany; phone 0049-(0)511-7638245 or 623151, FAX 0049-(0)511-7638606.

Ann Otol Rhinol Laryngol 100:1991

IMAGING CASE STUDY OF THE MONTH

MALIGNANT PARAGANGLIOMA WITH RETROGRADE FLOW IN THE INTERNAL CAROTID ARTERY

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INTRODUCTION

Marked displacement of the carotid artery and jugular vein is a regular feature associated with paragangliomas that arise in the neck (glomus vagale or carotid body tumors). Vascular invasion is rarely seen even with large tumors. A dramatic case of vascular invasion is presented.

CASE REPORT

A 38-year-old man was referred by the neurology service. Neurologic evaluation had demonstrated a marked lower-extremity peripheral neuropathy with a foot drop. The patient's neuropathy was believed to represent a neurologic paraneoplastic syndrome associated with a right-sided 6 x 3-cm upper neck mass. A complete radiographic evaluation was performed. Computed tomographic scanning demonstrated a large enhancing tumor in the right parapharyngeal space (Fig 1).

Arteriography was performed (Figs 2 and 3). The right common carotid injection demonstrated a large hypervascular mass filling from multiple branches of the right external carotid artery. The distal right internal carotid artery did not fill from the right common carotid injection. The right vertebral injection demonstrated multiple perforating vessels feeding the tumor, and showed filling of that portion of the right internal carotid artery distal to the tumor that did not show up on the right common carotid artery injection. Evaluation of the contralateral side demonstrated feeding vessels from the left external carotid artery. No feeding vessels were

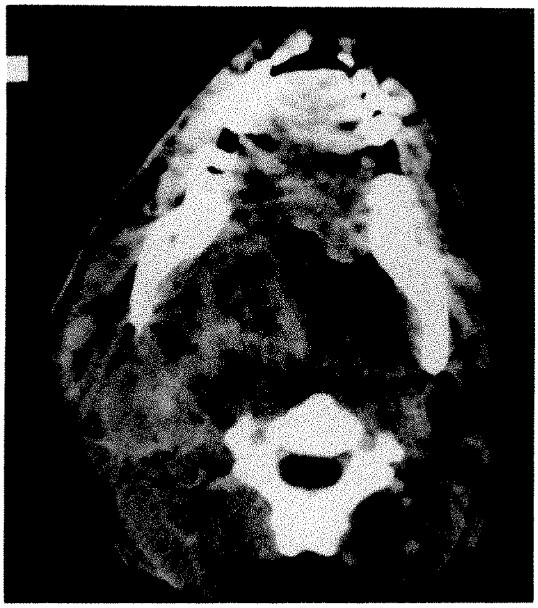

Fig 1. Axial computed tomogram demonstrating large right parapharyngeal space mass.

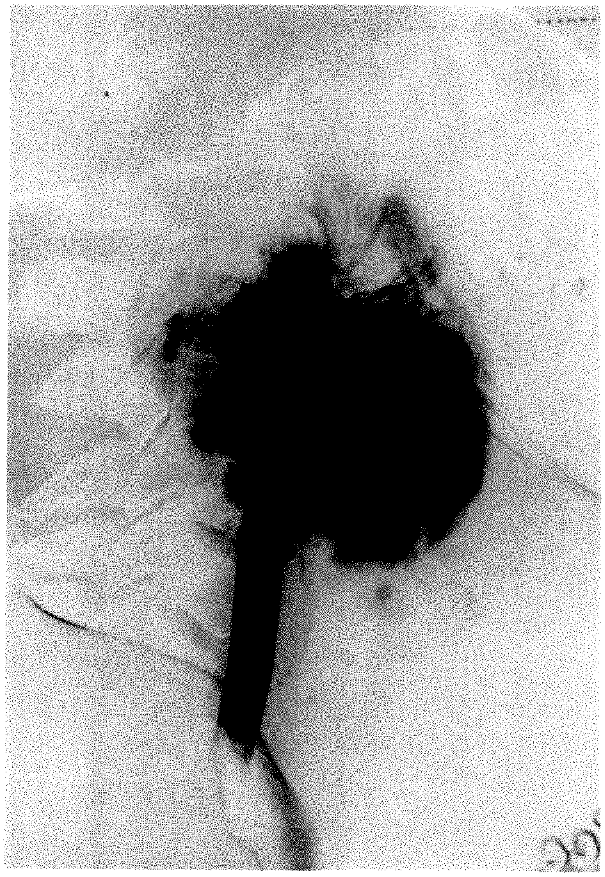

Fig 2. Right carotid injection. Large tumor stain can be appreciated. Internal carotid artery is occluded at level of vascular mass.

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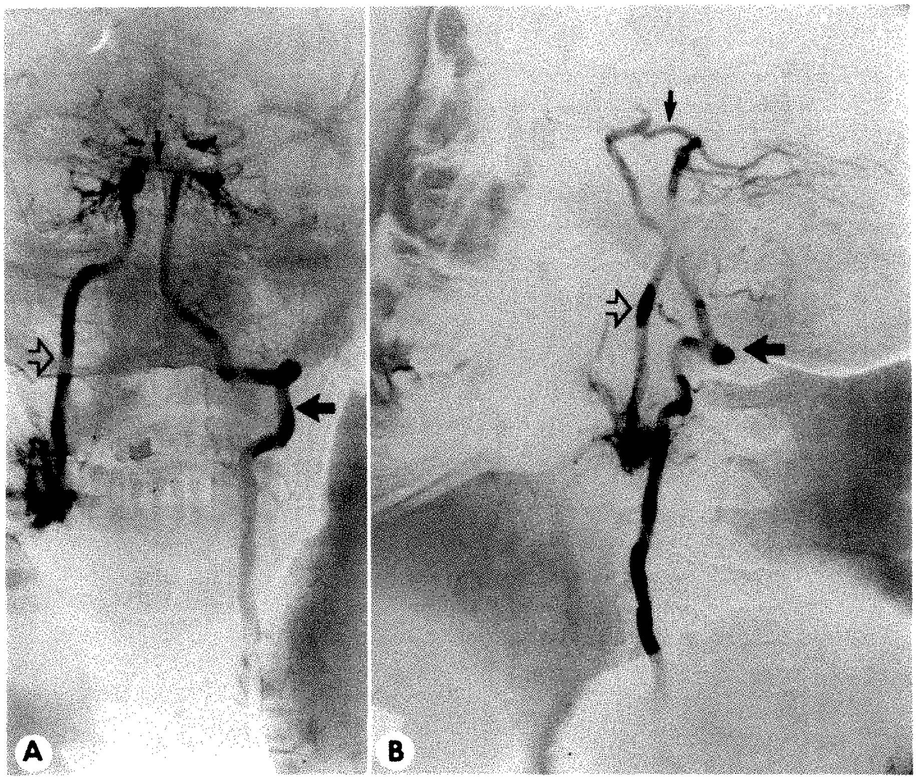

Fig 3. Left vertebral artery injection. Blood flows up vertebral artery (large solid arrow), through posterior communicating artery (small solid arrow), and down right internal carotid artery (hollow arrow) to supply blood to tumor. A) Anteroposterior projection. B) Lateral projection.

identified arising from the left vertebral artery when it was injected, but once again the distal right internal carotid was seen to fill retrograde.

In summary, feeding vessels arose from the right and left external carotid artery and from the right vertebral artery. Both the right and left vertebral artery injections resulted in retrograde filling of the occluded right internal carotid artery via the right posterior communicating artery. Moreover, the blood flowing retrograde within the right internal carotid artery had produced tumor staining; this finding indicates that it was nourishing tumor growth.

The patient underwent operative removal with considerable blood loss. Several cervical lymph nodes demonstrated partial replacement by paraganglioma, thus proving malignancy. The patient had a prolonged postoperative intensive care unit stay because of adult respiratory distress syndrome. Prior to discharge, a bone scan revealed multiple bony metastases. He was ultimately discharged from the hospital, but several days thereafter died at home of unknown causes.

DISCUSSION

The glomus vagale tumor was first reported in 1935 by Stout.[1] By 1977 an additional 125 cases of glomus vagale had been reported.[2] Glomus vagale tumors are paragangliomas that arise from the chemoreceptor tissue associated with the vagus nerve. The great majority arise in the area of the nodose ganglion.[3] They are much less frequent than paragangliomas of the carotid body or temporal bone and constitute only 2.5% of all paragangliomas.[4]

Generally these tumors surround but do not erode or invade associated vessels. Erosion or invasion of major vessels in a lesion with the radiographic appearance of a paraganglioma should raise the suspicion of malignancy, as noted previously by Biller et al,[3] who report the rate of malignancy in glomus vagale as 22%. However, Biller et al include as malignant two cases in which the only criterion for malignancy is histologic evidence of carotid artery invasion. Druck et al,[5] however, reported a similar rate of malignancy (19%) in glomus vagale tumors, using metastasis as the criterion of malignancy. Using metastasis as a criterion for malignancy, Someren and Karcioglu[2] reported 16% (8 of 48) of glomus vagale tumors as malignant. The incidence of malignancy appears to be significantly higher in glomus vagale tumors than paragangliomas of the temporal bone. Metastatic spread may be evidenced by distant or nodal metastasis. The most common sites for distant metastasis are lung, liver, and bone. Bony metastasis may be lytic or blastic, but lytic lesions are more common.[6]

CONCLUSIONS

Arteriographic evidence of invasion or occlusion of major arteries by a paraganglioma should raise suspicion of malignancy. Such angiographic findings warrant a preoperative metastatic work-up, because the presence of distant metastases will alter the therapeutic plan. When a malignancy is suspected, planned excision of the tumor should include neck dissection in order to remove associated cervical lymph nodes for pathologic examination. Neck dissection may be curative if disease is limited to regional nodes.

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INTERNATIONAL SYMPOSIUM ON GRAVES' OPHTHALMOPATHY

An International Symposium on Graves' Ophthalmopathy will be held Aug 23-24, 1991, in Amsterdam, the Netherlands. The symposium will bring together members from different disciplines interested in the management of Graves' ophthalmopathy. The program will include lectures, free communications, and posters on topics on surgical, medical, and radiotherapeutic management, on immunological aspects, and on classification of the eye changes. The deadline for submission of abstracts is June 1, 1991. For further information, contact Amsterdam Thyroid Club, c/o W. M. Wiersinga, MD, Dept of Endocrinology, F5-258, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

Ann Otol Rhinol Laryngol 100:1991

PATHOLOGY CONSULTATION

ORAL MONOMORPHIC ADENOMAS

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Monomorphic adenomas of the oral cavity have a predilection for the anterior mouth, particularly the upper lip. Two of the monomorphic adenomas, the inverted ductal papilloma and the canalicular adenoma, are biologically benign, but unfamiliarity with their histopathologic appearance can lead to a misdiagnosis of malignancy. The clinical and pathologic features of each are presented.

Two of the least familiar monomorphic adenomas of salivary glands are the inverted ductal papilloma of the oral cavity and the canalicular adenoma, also preponderantly an oral and/or labial tumor.

The inverted ductal papilloma bears a strong histologic similarity to the inverted (lateral wall) Schneiderian papilloma, but an absence of recorded

TABLE 1. ORAL INVERTED DUCTAL PAPILLOMA

Patients' age and sex	33 to 66 y; 4 men, 4 women
Oral site	2 mandibular vestibule; 2 buccal mucosa; 2 lips; 1 floor of mouth; 1 soft palate
Clinical size of lesion	1.5 to 1.0 cm
Recurrence or persistence	0 in follow-up periods of 6 y to 3 mo

Includes two cases from author plus review by Clark et al.[2]

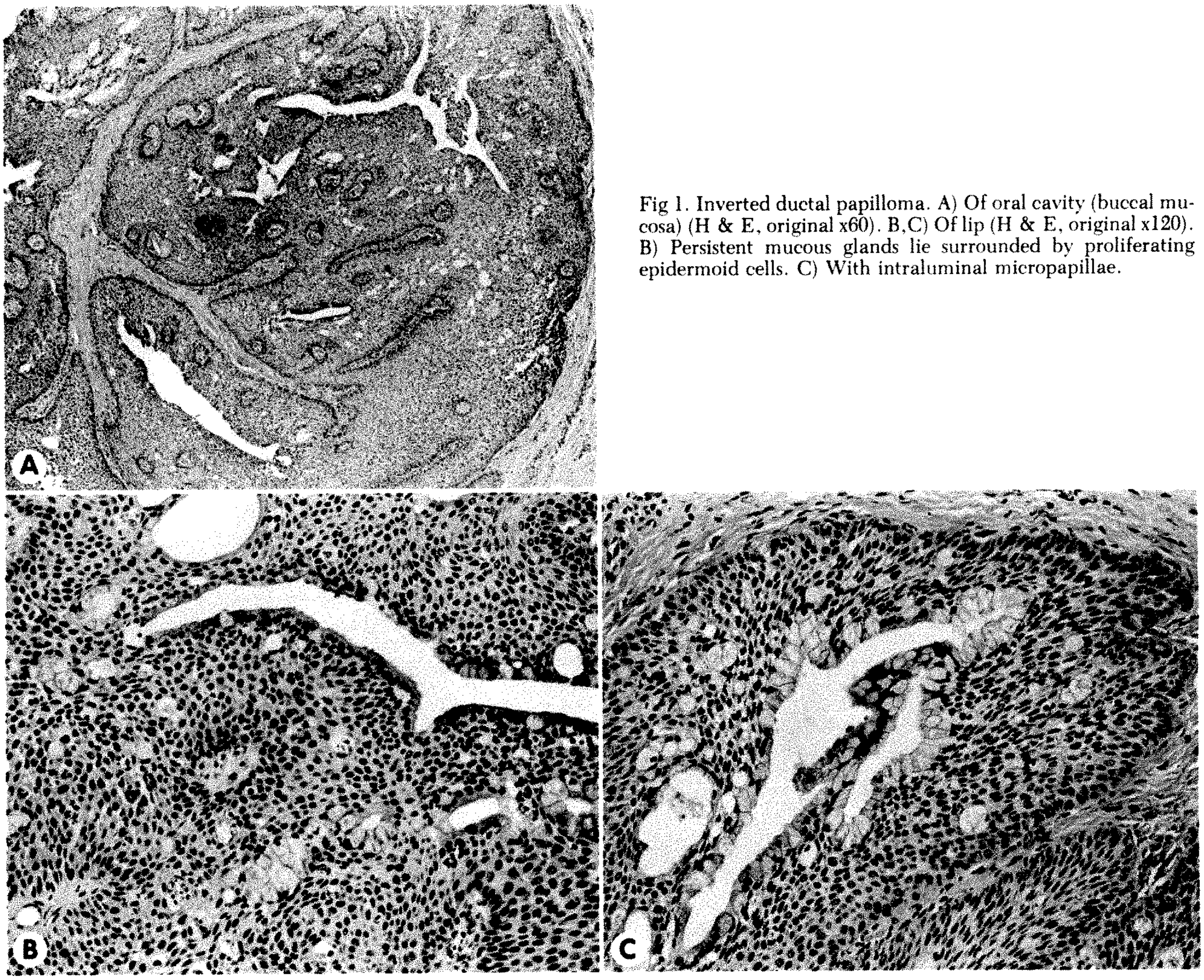

Fig 1. Inverted ductal papilloma. A) Of oral cavity (buccal mucosa) (H & E, original x60). B,C) Of lip (H & E, original x120). B) Persistent mucous glands lie surrounded by proliferating epidermoid cells. C) With intraluminal micropapillae.

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

TABLE 2. CANALICULAR MONOMORPHIC ADENOMA

Patients' age and sex	33 to 87 y; 33 men, 38 women
Oral site (where indicated)	61 lips (59 in upper); 7 buccal mucosa; 2 palate
Other salivary sites	3 parotid gland
Clinical size of lesion	1.5 to 0.5 cm
Recurrence or persistence	0 in follow-up periods of 10.6 y; 1 mo in 44 cases known or presumed to be canalicular monomorphic adenomas

From data presented by Daley et al[3] and Fantasia and Neville.[4]

recurrences or malignant transformation sets the oral papilloma apart from the Schneiderian papilloma.[1,2] An aberrant differentiation of salivary excretory duct reserve cells to an epidermoid rather than ductal epithelium is proposed for the histogenesis of the inverted ductal papilloma.[1,2]

As Table 1[2] indicates, the inverted ductal papilloma has a predilection for the anterior oral cavity, in which it presents as a soft, solid or cystic submucosal mass.

Microscopically, the lesion is circumscribed, always in a topographic relationship with minor salivary glands, and with or without continuity with the overlying mucosa (Fig 1A). An endophytic (inverted) growth pattern is seen in all cases. Origin from excretory ducts may be obscured by the epithelial proliferation. Epidermoid cells, rarely with keratinization, are the principal proliferating cell population (Fig 1B). Microcysts, isolated clusters of persistent mucous lining cells of ducts, and intraductal papillae are other features shared with the Schneiderian papillomas (Fig 1C). Cellular atypia or dysplasia, prominent mitotic activity, and necrosis should be absent.

The most important differential diagnosis is the mucoepidermoid carcinoma. The low-magnification, light optic inverting appearance of the papilloma is the key feature for exclusion of the carcinoma. The benign histologic features are paralleled by an innocuous clinical course (Table 1).

The canalicular adenoma is the most common monomorphic adenoma of the oral cavity, in which it has a pronounced proclivity for the upper lip (Table 2[3,4]). It may be regarded as nearly exclusively an oral and/or labial tumor.

Much like that of the inverted ductal papilloma, the canalicular adenoma's clinical appearance is re-

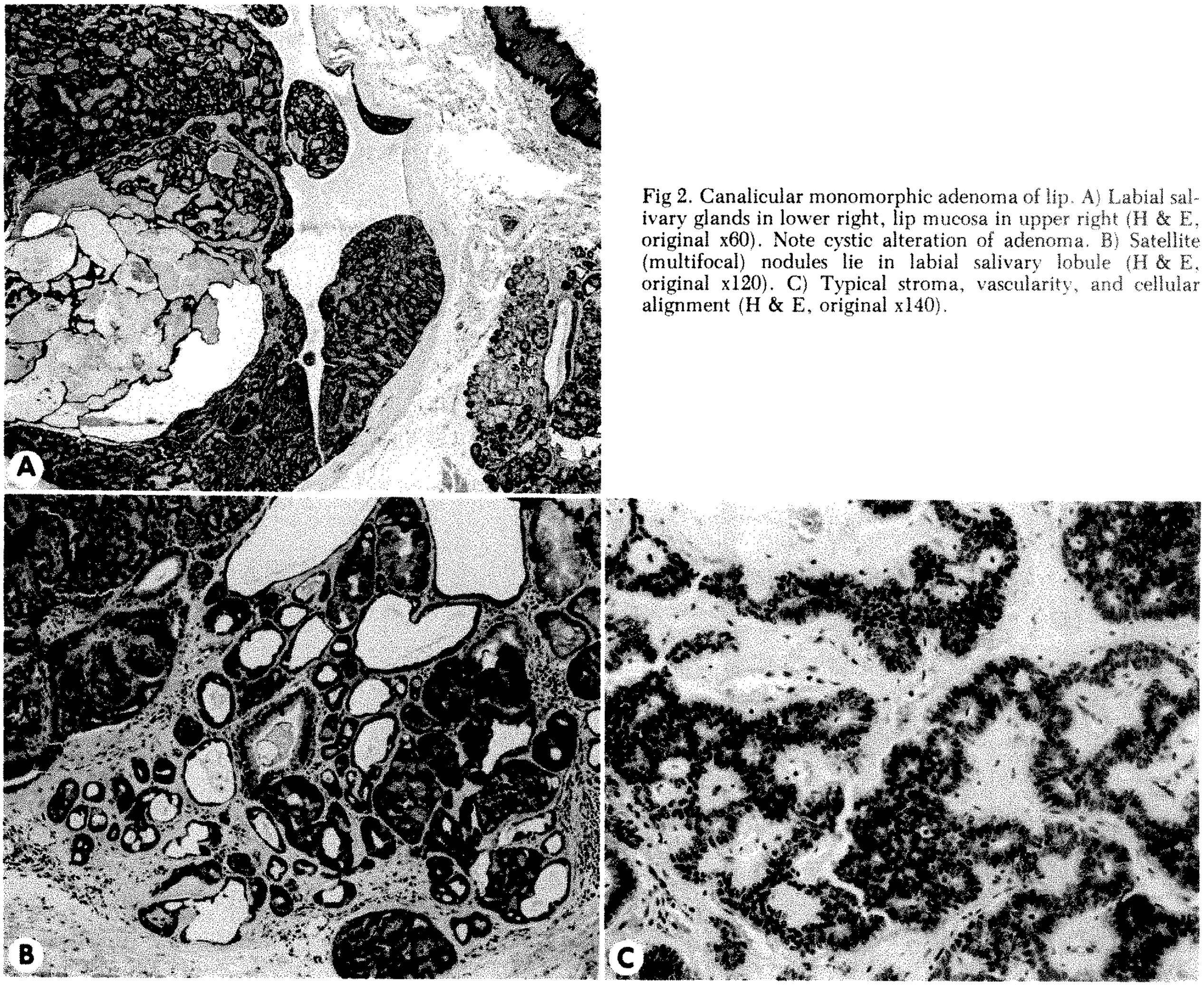

Fig 2. Canalicular monomorphic adenoma of lip. A) Labial salivary glands in lower right, lip mucosa in upper right (H & E, original x60). Note cystic alteration of adenoma. B) Satellite (multifocal) nodules lie in labial salivary lobule (H & E, original x120). C) Typical stroma, vascularity, and cellular alignment (H & E, original x140).

markably uniform. They present as submucosal swellings or nodules, are usually painless, and, unless traumatized, are not ulcerated. There may be a predilection for black patients, and most patients are over 50 years of age.

Biologically benign, the canalicular adenoma appears to have a low morbidity as far as recurrences are concerned. It should be noted, however, that follow-up information is often missing or covers relatively short periods. Unlike the inverted ductal papillomas, canalicular adenomas can be multifocal, thereby setting the stage for "recurrence" if the multifocal nodules are not encompassed in the first excision.

An apparent circumscription (Fig 2A) is sometimes belied by the separate micronodules and an incomplete encapsulation with "extracapsular" extension (Fig 2B). The parenchyma consists of hyperchromatic cuboidal to columnar cells in anastomosing ducts, canaliculi, and cords (Fig 2C). Cytoplasm is usually not abundant, and mitoses are never prominent unless there is secondary proliferation stimulated by a trauma-induced necrosis. Microcysts and macrocystic alteration of a poorly collagenized and mucohyaline stroma are typical of the canalicular adenoma. A delicate latticelike stromal vascularity can serve to distinguish the tumor from an adenoid cystic carcinoma. Stromal calcification and calcospherites are secondary features.

There are sufficient electron and light optic differences between the canalicular adenoma and other basaloid monomorphic adenomas to suggest origin from different parts of the salivary duct system for each type. Chen and Miller[5] consider the excretory duct cells to be precursors of the canalicular adenoma.

A low-grade adenocarcinoma is the most important differential diagnosis; adenoid cystic carcinoma, less so. The delicate vasculature, a parvicellular and often watery stroma with a uniform cell population arranged in nests, cords, and canaliculi surrounded by a well-defined basement membrane, point to an adenoma rather than adenocarcinoma.[6,7]

Adenomatoid hyperplasia of mucous salivary glands, a hyperplasia of normal-appearing mucinous acini with a considerable asymptomatic predilection for the palate, should not pose differential diagnostic problems.[8]

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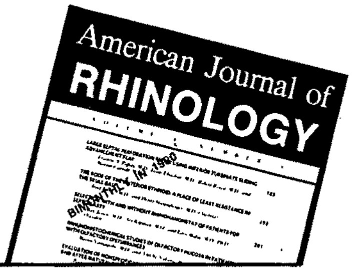

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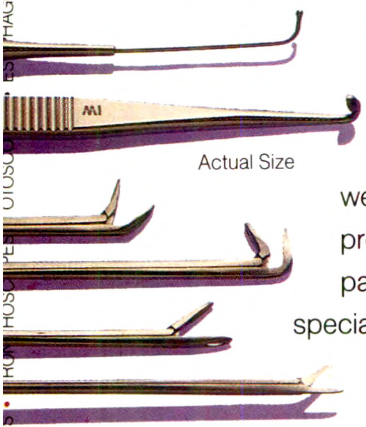

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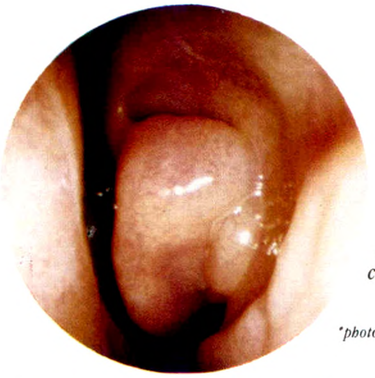

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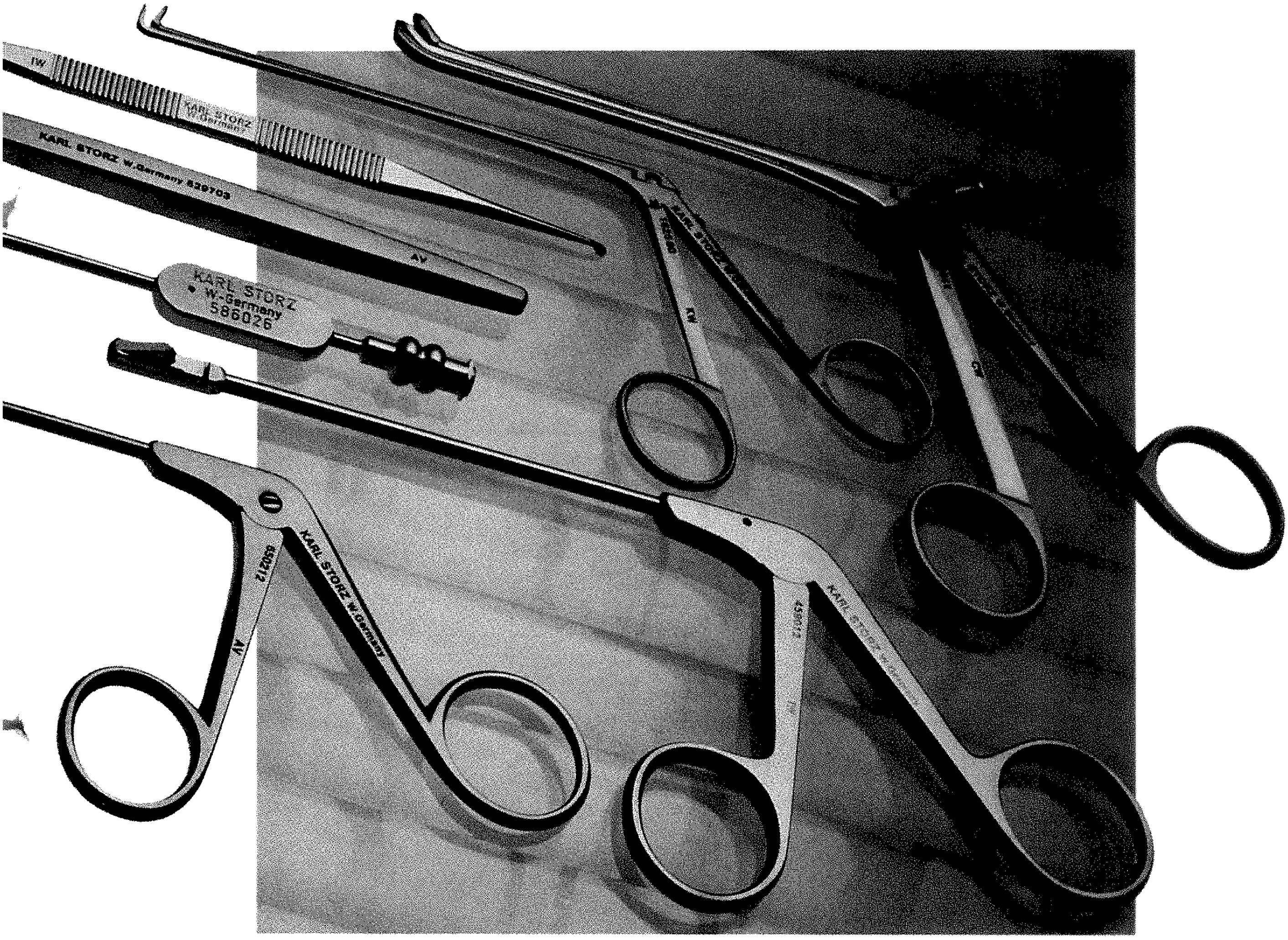
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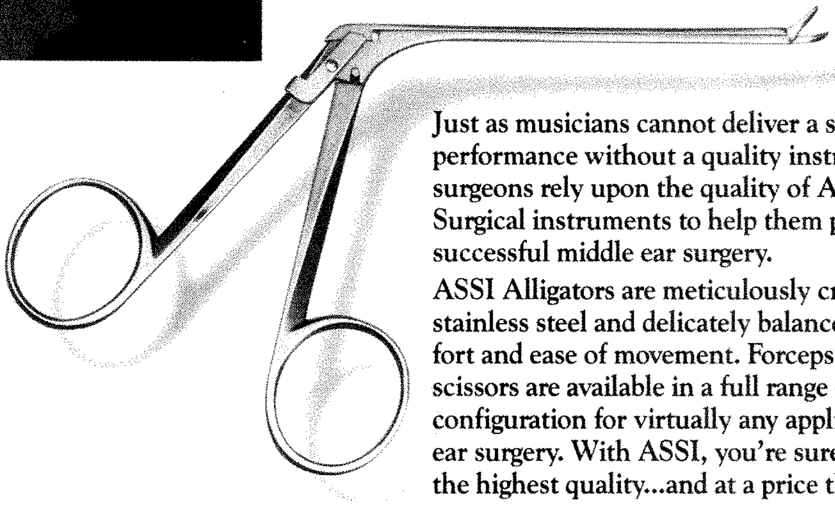

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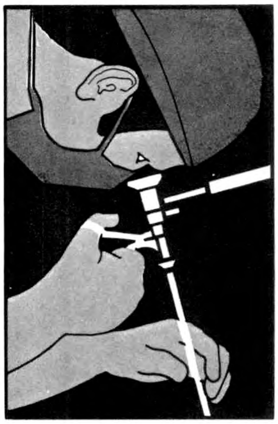

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ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY (ISSN 0003-4894) is published monthly by Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108. Second-class postage paid at St Louis, Mo. POSTMASTER: Send address changes to Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108.

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Ann Otol Rhinol Laryngol 100:1991

GLOBUS PHARYNGEUS: LONG-TERM FOLLOW-UP AND PROGNOSTIC FACTORS

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DUBLIN, IRELAND

A prospective trial of 80 patients with globus pharyngeus is reported. An in-depth analysis of the typical history at presentation is given. The average follow-up period was 27 months (range, 21 to 42 months). The asymptomatic rate at this interval was 25%, with a further 35% reporting a significant improvement in symptoms. Three independent factors were found to influence prognosis ($p < .05$). These were sex, length of history at consultation, and the presence or absence of associated throat symptoms. Male patients having a history of the globus symptom for less than 3 months and not complaining of any associated throat symptoms had the best chance of becoming asymptomatic or symptomatically improved. The presence or absence of heartburn or its treatment had no bearing on outcome.

KEY WORDS — globus pharyngeus, outcome, prognostic factors.

INTRODUCTION

Globus pharyngeus is a common disorder, comprising between 3% and 4.1% of new otolaryngology outpatient referrals.[1,2] The condition was first noted by Hippocrates[3] 2½ thousand years ago. It was then regarded as a disease occurring exclusively in women, being linked with dysfunction of the uterus, from which it was believed all hysteria was derived. John Purcell[4] in 1707 was the first to describe the condition accurately. He believed the sensation of a hard ball in the throat was due to contraction of the neck strap muscles pressing on the thyroid cartilage. In 1794 the term "globus hystericus" was defined in the Oxford University Dictionary as "a choking sensation, as of a lump in the throat to which hysterical persons are subject."

Malcomson[1] in 1968 was the first to use the term "globus pharyngis," feeling that globus hystericus indicated a diagnosis that was often wrong. More recently, there is a general acceptance that the condition is not merely a reflection of a hysterical disorder, but is related to an underlying disorder of the upper gastrointestinal tract. Despite this recent better understanding, no study to date has determined accurately the proportion of patients who will become asymptomatic over a prolonged period of time. Neither has any author managed to associate the symptoms at presentation of globus pharyngeus with eventual outcome.

It was for these reasons we initiated the present prospective trial, the aims of which were, first, to define the clinical features of globus pharyngeus; second, to determine the percentage of patients who will become asymptomatic or symptomatically improved at long-term review; and last, and unique to this study, to identify factors in the history of the patients that are associated with a better prognosis.

MATERIALS AND METHODS

A total of 83 patients presenting to the otolaryngology outpatient department of the Royal Victoria Eye and Ear Hospital, Dublin, between February 1985 and December 1986, complaining of a sensation of a "lump in the throat" were eligible for study. Histories were taken and a comprehensive examination including a personality profile was performed on each patient. All patients were investigated with chest x-ray study, lateral soft tissue x-ray study of the neck, barium swallow study with tilt, and, where thought necessary, endoscopic examination of the upper gastrointestinal tract and upper airway. If the results of these investigations were normal, 24-hour pH monitoring was performed along with manometry of the upper and lower esophageal sphincters.

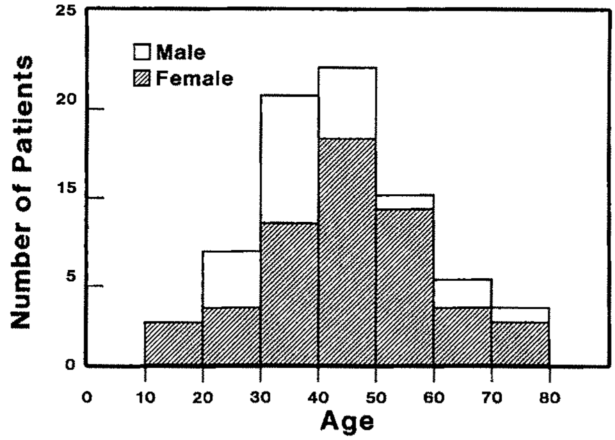
After excluding an identifiable cause for the initial presenting complaint, the diagnosis of globus pharyngeus was made. Patients were managed by a clear explanation of the condition and reassurance. Those patients with significant reflux esophagitis were in addition advised on general measures to decrease gastric acid reflux and treated with specific antireflux medication, namely cimetidine and Gaviscon. All patients were followed on a regular basis for an average period of 27 months (range, 21 to 42 months).

Results were entered onto a computer and assessed in the statistics department of Trinity College, Dublin. Exploratory analysis was performed with the Statistix statistical package. Significant relationships between clinical findings and treatment outcome were sought by use of discrete Poisson regression.

RESULTS

Of 83 patients entered into the trial, 3 patients

From the Department of Otolaryngology, St James's Hospital (Timon, O'Dwyer, Walsh), and the Department of Statistics, Trinity College (Cagney), Dublin, Ireland.



Numbers of male and female patients by age.

with definite disorders, namely base of tongue tumor, antrochoanal polyp, and chronic sinusitis, were excluded, leaving 80 patients for subsequent study. Of these, 7 patients were lost to follow-up, leaving 73 patients available for analysis, 4 of whom had incomplete data recorded.

Clinical Features. The average age at presentation was 43 years (range, 14 to 75 years), and the male to female ratio was 1 to 2.3. This female predominance was present through all age groups (see Figure). The patients complained of a "lump in the throat" for a mean period of 8.5 months (range, 2 weeks to 4 years) before attending the otolaryngology outpatient department. The site of the "lump in the throat" was between the thyroid cartilage and root of the neck in 86% of cases, and placed in the midline in 80% of patients. In 56% of patients the onset of symptoms was sudden; however, in only 9% of patients was there a clearly related preceding event. Patients were asked to grade persistence of their symptoms into continuous, fluctuating, intermittent, or occasional presence of the "lump." Results showed a near-equal division between each group apart from a slight preponderance in the continuous group. Dry swallowing made the globus symptom worse in 33% of patients, while food swallowing eased the globus symptom in 36% of patients.

Associated Symptoms. Throat symptoms, most commonly dryness and constant clearing of the throat, were complained of by 74% of patients. Swallowing disorders, namely food sticking and food holdup, were present in 35% of patients, while heartburn was complained of by 55% of patients.

Follow-up. Review at a mean period of 27 months (range, 21 to 42 months) showed an asymptomatic rate of 25%, with significant improvement in symptoms in a further 35% of cases. This left 36% of patients reporting no change in symptoms, while 4% complained that the globus symptom had become more pronounced.

Prognostic Factors. The prognostic factors evaluated were age of patient, sex, length of history, onset, associated throat symptoms, swallowing difficulties and heartburn, arytenoiditis seen on clinical examination, and personality. For statistical purposes, patients were divided into two groups according to the outcome of the globus symptom. Patients who were asymptomatic or symptomatically improved were compared with patients who had no change or worsening of the condition. By regression analysis three prognostic factors were isolated, namely sex of patient, length of history at the time of presentation, and presence or absence of associated throat symptoms ($p<.05$). No interactions were found between these significant factors, so the independence model was chosen. The Table shows cross-tabulation of these three factors with clinical outcome. On the basis of these findings the patients with the best prognosis are males with a history of "lump in the throat" for less than 3 months who do not complain of any associated throat symptoms. Conversely, female patients with a history longer than 3 months complaining of associated throat symptoms have the worse outcome.

CLINICAL OUTCOME

	No. of Patients	
	Cured or Improved	*No Change or Worse*
Sex (n = 73)		
Male	17	5
Female	27	24
Length of history (n = 70)		
<3 mo	17	5
>3 mo	26	22
Associated throat symptoms (n = 69)		
No	14	5
Yes	27	23

DISCUSSION

Globus pharyngeus is a diagnosis of exclusion, based on a typical history after excluding other disorders. By definition, findings on physical examination are essentially normal. The cause of globus pharyngeus is unknown and is probably multifactorial. True hysteria is rare among patients with this condition.[5] Aside from hysteria, many other conditions have been considered in its causation. These include cervical osteophytes, sinusitis, temporomandibular joint dysfunction, cricopharyngeal spasm, and enlarged lingual tonsils. Several authors feel the "lump in the throat" is a normal mechanism provoked by strong emotion.[6,7] According to the results of a questionnaire, nearly half of the 147 normal subjects asked reported having experienced the globus symptom in association with strong emotion.[8] More recently, gastroesophageal reflux has been implicated. Batch[9,10] found evidence of acid reflux in 60% of his patients. However, Moloy and Charter[2] found significant acid reflux in only 38% of their cohort, compared to 36% of the general population. In our investigation, barium swallow study with tilt and esophagoscopy showed evidence of reflux esophagitis in 40% of patients. Together with the results of 24-hour pH monitoring, which was performed in 44 patients, the overall rate of acid reflux was 52%, comparing favorably with Batch's results.[9,10]

The general characteristics of the patients in this study were similar to those found in previous reports.[9-11] The mean age at onset was 43 years, compared to 45.2 years in Batch's paper.[9] Women are more likely to suffer from globus pharyngeus.[2,5,9,10] Moloy and Charter[2] found that although women were affected three times more commonly in the age group less than 50 years, there was an equal distribution above 50 years of age. We were unable to confirm this finding. In this study, women in all age groups were more commonly affected, in accord with the findings of Batch[9,10] and Pratt et al.[5]

In three quarters of the patients in this report the "lump" was localized in the midline and between the suprasternal notch and thyroid cartilage. On the basis of these findings, one should be more suspicious of an underlying organic lesion in patients whose symptoms are not in keeping with this anatomic distribution. Batch[9,10] reported that the "lump" was aggravated by dry swallowing and improved by food swallowing. This combination was present in 60% of his patients. However, these findings were found in only one third of our cohort, and although this combination is helpful in making the diagnosis, it cannot be relied upon. Other factors that we found to aggravate the globus symptom in many patients were stress and alcohol ingestion.

Although the "lump in the throat" is the chief symptom and presenting complaint, in 75% of our patients there were associated throat symptoms. True dysphagia and weight loss were conspicuous by their absence. These are the most characteristic negative (ie, usually absent) features of the condition.[1] Nonetheless, swallowing difficulties such as food sticking are commonly associated with globus pharyngeus[9,10] and were complained of by one third of our patients. Irritable bowel syndrome is a functional disorder of the gastrointestinal tract, as is globus pharyngeus. It is a common condition, present in approximately one in seven of the general population.[12] Watson et al[13] reported that globus pharyngeus was common in patients with irritable bowel syndrome. However, we were unable to demonstrate such a relationship.

The cure rate in this study, despite in-depth investigation and treatment, was a disappointing 25% at an average follow-up period of 27 months. This asymptomatic rate is markedly less than that of previously reported cure rates.[2,9,10,11,14] Moloy and Charter[2] claimed that 79% of their 103 patients became symptom-free, with 53% of these patients cured by assurance alone. However, no follow-up period is specified in their paper. Freeland et al[11] reported a cure rate of 77% in the 124 patients they followed for periods between 6 months and 3 years, but no average review period was given. We feel this difference in cure rates arises for the following reasons. First, our patients were followed for a substantially longer period of time than those in previous reports. Second, although only 25% of patients in this study became asymptomatic, a further 35% reported that their symptoms had significantly improved. Hence, our overall improved or cure rate of 60% compares favorably with cure rates claimed by previous authors. Of importance, many of the patients with an improvement in symptoms noted that the feeling of a "lump in the throat" fluctuated, with periods of weeks to months free of symptoms. We therefore suspect that previous studies with short-term follow-up classified this group of patients as cured, obtaining a falsely high asymptomatic rate.

This is the first report to identify independent prognostic factors that alter the outcome of globus pharyngeus. Only four patients had all the favorable prognostic indicators. Three of these patients became asymptomatic, and one reported marked improvement of the condition.

Of 17 patients with all three unfavorable prognostic factors, one patient reported complete resolution of symptoms. Freeland et al[11] reported finding red, edematous arytenoids in 20% of patients with globus pharyngeus, and these responded readily to treatment. In this study, 12 of the 80 patients (15%) had erythematous arytenoids; nevertheless, the presence of erythema had no effect on the outcome of the disorder. The presence or absence of heartburn, of proven gastroesophageal reflux, or of treatment of acid reflux was not statistically significant when compared to outcome. Of patients who complained of heartburn, most reported an improvement of this symptom with antireflux measures but with no concomitant relief of the "lump in the throat." This is highlighted by one patient who required fundoplication for severe reflux esophagitis, with subsequent relief, but reported no improvement in the globus symptom.

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EFFECT OF OTOTOXIC DRUG ADMINISTRATION TO THE ENDOLYMPHATIC SAC

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SEOUL, SOUTH KOREA

ROBERT S. KIMURA, PHD
BOSTON, MASSACHUSETTS

Aminoglycosides were applied to the endolymphatic sac of guinea pigs, and the inner ears were studied by light microscopy. In group 1 gentamicin sulfate application on the lateral surface of the endolymphatic sac produced sensory cell atrophy limited to the macula sacculi. In group 2 gentamicin injection into the sac by extradural and intradural approaches often showed lesions in the maculae sacculi and utriculi, cristae of the three ampullae, and organ of Corti in the basal turn. In group 3 passive instillation of streptomycin sulfate pellets into the sac from a lateral opening resulted in a similar pattern of degeneration but with less severity in comparison to the injection method. Mild to severe endolymphatic hydrops was sometimes observed. The study shows diffusion of drugs taking place against the longitudinal flow of endolymph. This procedure may be applicable for the treatment of Meniere's disease.

KEY WORDS — cochlea, endolymphatic sac, gentamicin, guinea pig, Meniere's disease, streptomycin, vestibular labyrinth.

INTRODUCTION

Various medical and surgical treatments have been used in attempts to control the incapacitating vertigo and fluctuating hearing loss associated with Meniere's disease. Although aminoglycosides primarily affect the inner ear sensory cells, these drugs also affect the structures involved with the production of endolymph.[1] Streptomycin sulfate is known to be more toxic to the vestibular sense organs than to the organ of Corti,[2] and has been used effectively in the treatment of incapacitating vertigo caused by Meniere's disease.[3-5] Routes of ototoxic drug administration have varied from systemic injection to topical intratympanic[6,7] and lateral semicircular canal[8-10] application for the purpose of unilateral vestibular ablation. Another possible site for ototoxic drug application is the endolymphatic sac. During endolymphatic sac decompression procedures, ototoxic drugs could be applied to the endolymphatic sac. Despite the controversy concerning the rate of flow, it is the general consensus that endolymph longitudinally flows toward the endolymphatic sac. The questions raised are whether a drug applied to the endolymphatic sac can reach the vestibular labyrinth against the flow of endolymph, and what effect this application will have on the inner ear sensory structures. In the present study, small amounts of the well-known ototoxic aminoglycosides streptomycin sulfate and gentamicin sulfate were applied to the endolymphatic sac of guinea pigs to resolve these questions.

MATERIALS AND METHODS

A total of 33 albino guinea pigs weighing 250 to 300 g with good pinna reflexes were used in this study. The animals were anesthetized by intraperitoneal injection of sodium pentobarbital (35 mg/kg) and were operated on under sterile conditions. The endolymphatic sac was approached through the extradural posterior cranial fossa route. A coronal scalp incision was made and the muscles attached to the lambdoid suture line were elevated. Occipital and lateral protuberances of the occipital bone over the sigmoid sinus were thinned with a diamond bur. The thinned bone was removed with fine forceps and picks. After careful blunt dissection of the sigmoid sinus from its sulcus, the sigmoid sinus was displaced medially. Small pieces of Gelfoam and cotton wick were gently inserted under the sigmoid sinus until the cranial aperture of the endolymphatic sac was visualized. Since the endolymphatic sac extends from the cranial aperture of the vestibular aqueduct toward the sigmoid sinus, great care was taken not to damage the sigmoid sinus or dura.

Three different procedures were used for drug application. In group 1, consisting of eight guinea pigs, about 10 μL (40 mg/mL) of gentamicin sulfate was applied to the lateral surface of the endolymphatic sac. In group 2, consisting of eight animals, about 10 μL of gentamicin sulfate was slowly injected into the endolymphatic sac via a glass micropipette with microinjection equipment. The hole was larger than the tip of the micropipette and overflow of the injected solution could be seen. In group 3 streptomycin sulfate was used instead of gentamicin sulfate. The initial result of group 1 indicated a need for an increase in the drug concen-

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From the Department of Otolaryngology, Korea University, Seoul, South Korea (Lee), and the Department of Otology and Laryngology, Harvard Medical School (Kimura), and the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary (Kimura), Boston, Massachusetts. Supported by National Institutes of Health/National Institute on Deafness and Other Communication Disorders grant HAR 8 R01 DC 00073-28. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Massachusetts Eye and Ear Infirmary.

Presented at the Research Forum of the American Academy of Otolaryngology–Head and Neck Surgery, New Orleans, Louisiana, September 24-28, 1989.

REPRINTS — Robert S. Kimura, PhD, Dept of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

TABLE 1. GENTAMICIN SULFATE APPLICATION ON SURFACE OF ENDOLYMPHATIC SAC (GROUP 1)

Specimen No.	*Cochlear Turn*				*Spiral Ganglion*	*Stria Vascularis*	*Reissner's Membrane*	*Saccule*	*Utricle*	*Crista Ampullaris*		
	1	*2*	*3*	*4*						*Sup*	*Lat*	*Post*
1*	—	—	—	—	—	—	—	D	d	—	—	—
2	—	—	—	—	—	—	—	d (spot)	—	—	—	—
3	—	—	—	—	—	—	—	—	—	—	—	—
4	—	—	—	—	—	—	—	—	—	—	—	—
5	—	—	—	—	—	—	—	—	—	—	—	—
6	—	—	—	—	—	—	—	d	—	—	—	—
7*	—	—	—	—	—	—	—	d (spot)	—	—	—	—
8	—	—	—	—	—	—	—	—	—	—	—	—

D — moderate to severe degeneration, d — slight degeneration.

*Endolymphatic sac was opened.

tration. The strength of streptomycin sulfate can be more easily regulated than that of gentamicin, since it comes in powder form rather than in solution. In 17 animals, a small hole was made around the cranial aperture of the vestibular aqueduct with a sharp pick. Four to five tiny pellets or powder balls of streptomycin sulfate were gently placed in the lumen of the endolymphatic sac. These pellets were made by moistening streptomycin powder in distilled water. The approximate total dosage applied on the endolymphatic sac was 16 to 20 μg. No attempt was made to pack the drug inside the sac. After administration of the drugs into the endolymphatic sac, the defect in the occipital bone was covered with a large piece of Gelfoam. The neck incision was repaired layer by layer. In two control animals, the endolymphatic sac was exposed without drug application.

One month after the drug applications, all animals were deeply anesthetized with pentobarbital and were killed painlessly by intracardiac perfusion of Heidenhain-Susa. The temporal bones were removed, decalcified, embedded in celloidin, and serially cut at 20-μm thickness. Every 10th section was stained with hematoxylin and eosin for light microscopic examination.

RESULTS

In the first group, in which gentamicin sulfate was applied to the surface of the endolymphatic sac, the ototoxic lesions of the inner ear sensory structures were not remarkable. Among the eight guinea pigs, four specimens (50%) showed slight degeneration of the sensory cells of the macula sacculi. In two of these four specimens (Nos. 1 and 7) the endolymphatic sac was accidentally opened; one of them also showed degeneration of the macula utriculi. No sensory cell lesions were found in the cochlea or cristae ampullares in this group (Table 1).

In the second group, in which gentamicin sulfate was injected directly into the endolymphatic sac, sensory cell lesions occurred more frequently and were the most severe of the three groups. Among the vestibular sensory structures, the most common and severe lesions were found in the macula sacculi (88% of specimens), followed by the macula utriculi (75%) and superior, lateral, and posterior cristae (63%). The three cristae showed nearly the same degree of degeneration. In the cochlea, sensory lesions were found in 63% of the specimens. The basal turn was most frequently affected (63%), followed by the apical turn (38%) and second and third turns (25%). Degeneration of the spiral ganglion, which coincided with severe sensory cell degeneration of the cochlea, was found in four specimens (50%). Two specimens (Nos. 13 and 16) had hydrops in the cochlea and saccule; they showed slight obstructive lesions in the endolymphatic duct and sac (Table 2). Two specimens (Nos. 12 and 13) showed severe concomitant sensory cell lesions in all cochlear turns and all vestibular sense organs, and two others (Nos. 9 and 16) showed small lesions, about 3 to 4 mm, in the basal turns associated with severe lesions in all vestibular sense organs. Two

TABLE 2. GENTAMICIN SULFATE INJECTION INTO ENDOLYMPHATIC SAC (GROUP 2)

Specimen No.	*Cochlear Turn*				*Spiral Ganglion*	*Stria Vascularis*	*Reissner's Membrane*	*Saccule*	*Utricle*	*Crista Ampullaris*		
	1	*2*	*3*	*4*						*Sup*	*Lat*	*Post*
9*	D	—	—	—	D1	—	—	D	D	D	D	D
10	—	—	—	—	—	—	—	—	—	—	—	—
11	d	—	—	D	D4	—	—	d	d	d	d	d
12	D	D	D	d	D1-4	—	—	D	D	D	D	D
13	D	D	D	D	D1	D1-4	H1,4	D/H	D	D	D	D
14	—	—	—	—	—	—	—	d	d	—	—	—
15	—	—	—	—	—	—	—	D	—	—	—	—
16*	D	—	—	—	—	—	h1	D/h	D	D	D	D

D — moderate to severe degeneration, d — slight degeneration, H — moderate to severe endolymphatic hydrops, h — slight hydrops, 1 — basal turn, 2 — second turn, 3 — third turn, 4 — apical turn.

*Injection through intracranial route.

TABLE 3. STREPTOMYCIN SULFATE PELLET INSTILLATION INTO ENDOLYMPHATIC SAC (GROUP 3)

Specimen No.	*Cochlear Turn*				*Spiral Ganglion*	*Stria Vascularis*	*Reissner's Membrane*	*Saccule*	*Utricle*	*Crista Ampullaris*		
	1	*2*	*3*	*4*						*Sup*	*Lat*	*Post*
17	D	—	—	—	—	Dl	H1-4	D/H	D	D	D	D
18	—	—	—	—	—	—	—	d	—	—	—	—
19	D	D	—	—	D1,2	—	—	D/h	D	D	D	D
20	—	—	—	—	—	—	—	—	—	—	—	—
21	d	—	—	—	—	—	H1,4	D/H	d	d	D	d
22	—	—	—	D	—	—	h1,4	D/H	—	—	—	d
23	—	—	—	—	—	dl	h1,4	H	h	—	—	—
24	—	—	—	d	—	—	H1,4	H	H	—	—	—
25	d	—	—	d	—	—	—	D	D	D	D	D
26	—	—	—	—	—	—	—	—	—	—	—	—
27	—	—	—	—	—	—	—	h	h	—	—	—
28	d	—	—	—	—	—	—	H	H	—	—	—
29	—	—	—	—	—	—	—	D/h	—	—	—	—
30	d	—	—	—	—	—	—	d	—	d	—	d
31	D	D	D	D	D1-4	Dl	—	D	D	D	D	D
32	d	—	—	—	dl	—	—	D	D	D	D	D
33	d	—	—	d	d4	—	H1-4	D/H	d/H	—	—	—

D — moderate to severe degeneration, d — slight degeneration, H — moderate to severe endolymphatic hydrops, h — slight hydrops, 1 — basal turn, 2 — second turn, 3 — third turn, 4 — apical turn.

specimens did not show any lesions in the cochlea, but showed lesions in the saccule and the saccule and utricle, respectively.

In the third group, in which streptomycin sulfate powder or pellets were placed into the endolymphatic sac, cochlear and vestibular lesions were also common. The vestibular sensory cell lesions were shown most frequently in the macula sacculi (65%), followed by the posterior crista (47%), the macula utriculi (41%), and the superior (41%) and lateral (35%) cristae. Six specimens showed lesions in all vestibular sense organs. Of the three cristae, the posterior crista was most frequently affected. In the cochlea, the lesions were most common (53%) at the basal end (mostly in the 1- to 2-mm area), followed by the apical (29%), second (12%), and third (6%) turns. In one specimen (No. 31) extensive sensory cell degeneration occurred in both cochlear and vestibular systems (Table 3). When the sensory cells of the basal turn were degenerated, most of the sensory cells of the vestibular labyrinth were affected (Fig 1). Only one specimen showed lesions in the basal turn and no degeneration in the vestibular labyrinth. In two specimens (Nos. 18 and 29) lesions were observed only in the saccule and not in the organ of Corti. Hydrops was shown in the saccules of 10 specimens (59%), in the cochleas of 6 (35%), and in the utricles of 5 (29%). Pink precipitate and the number of floating cells in the endolymphatic sac were decreased after ototoxic drug administration into the sac.

The sense organs of the two control animals were normal. Surgical incision of the endolymphatic sac at the region of the operculum also failed to produce lesions in the sensory cells of the guinea pig inner ear.[11]

DISCUSSION

Streptomycin application produces lesions primarily in the vestibular sense organs, while gentamicin affects both cochlear and vestibular sense organs, with more severe lesions occurring in the vestibular labyrinth.[12] In our previous studies gentamicin was administered transtympanically and in the lateral canal.[9] Compared to the lesions in these studies, gentamicin application on both opened and unopened lateral walls of the endolymphatic sac (group 1) produced very small lesions. In order to increase the magnitude of the lesions, gentamicin was injected into the sac (group 2) in spite of the risk of the injection's forcing the drug toward the cochlea. Alternatively, the effect on the inner ear can be enhanced by raising the concentration of the drug in the sac by increasing the number of drug pellets, as in group 3. In this study the precise dosage of drugs entering the sac, either by gentamicin injection or streptomycin instillation, cannot be determined. The important finding from this study is that in spite of differences in drugs, dosage, and mode of application, the overall patterns of sensory cell degeneration in the cochlea and vestibular labyrinth were similar in groups 2 and 3 (Fig 2). In both groups, the sensory cells of the macula sacculi were the most vulnerable. The sense organs in group 2 were more often affected than those in group 3. This finding does not necessarily imply that gentamicin is more toxic than streptomycin, however, since the modes of drug application were different.

In group 1, small sensory cell lesions were found in the macula sacculi. Since simple opening of the endolymphatic duct or sac does not produce lesions in the saccule,[11] the lesions seen in the present study are probably due to the effect of gentamicin. The route of drug penetration could be through the perisaccular or periductal tissue or even the endolymphatic space. It is unlikely that the drug reached the sensory cells through the cochlear aqueduct, since the cochlear sensory cells were not affected by drug

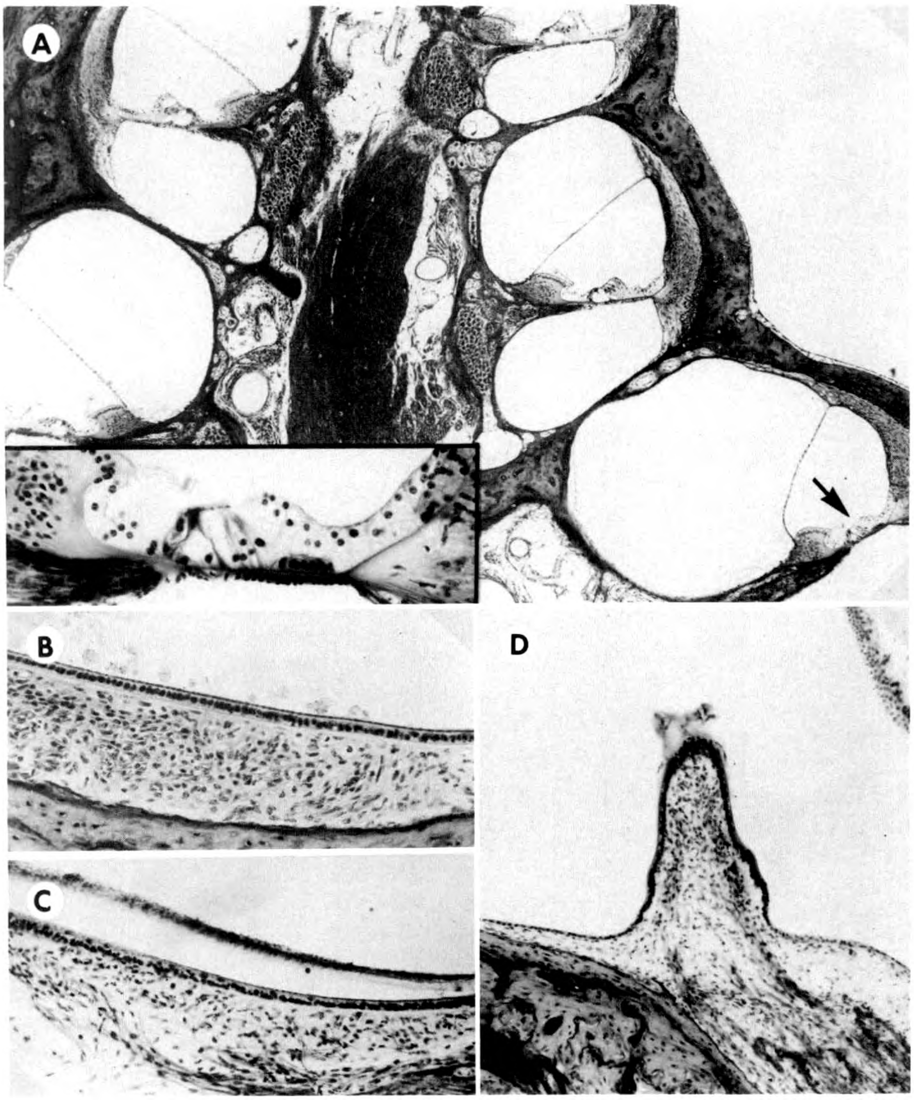

Fig 1. (Specimen 25, group 3) Extent of degeneration of cochlear and vestibular sensory cells is shown 1 month after passive instillation of streptomycin sulfate into endolymphatic sac. A) Cochlea shows outer hair cell degeneration and slight endolymphatic hydrops in basal turn. Inset) Higher-power view of organ of Corti (arrow) shows outer hair cell degeneration. Vestibular sensory cells were degenerated in B) macula sacculi, C) macula utriculi, and D) lateral crista ampullaris.

application on the lateral surface of the endolymphatic sac. The fact that the lesions were confined to the saccule with no damage to the cochlea and cristae suggests that drugs can diffuse to the sense organs located near the internal aperture of the endolymphatic duct, but that drug concentration is not sufficient to affect sense organs located further away. The drugs cannot easily penetrate the epithelial cells of the endolymphatic sac or pass through the vestibular aqueduct.

Systemic injection of streptomycin into cats primarily affected the sensory epithelium of the cristae ampullares with little or no injury to the utricle or saccule.[13] In groups 2 and 3 of this study, in which drugs were injected directly into the endolymphatic sac, lesions of various degrees were found in the sensory cells of the maculae sacculi and utriculi as well as in the cristae and organ of Corti. These discrepancies may be due to differences in animal species and the routes or dosages of drug application. In the cochlea, lesions in the sensory cells of the basal turn were the most common, followed by lesions in the apical turn. It was anticipated that lesions might be found in the sensory cells of the basal end of the cochlea; however, it was unexpected that sensory cell degeneration occurred more often in the apical turn than in the second or third turn. Kohonen[14] observed similar patterns of lesions in his study on aminoglycoside ototoxicity. This finding could be due to slow absorption of the drugs at the cupular cecum of the cochlear duct. The stria vascularis at the cochlear apex is smaller and there is less vascularity. Various degrees of endolymphatic hydrops were observed in both groups 2 and 3. This finding was more or less expected, since the endolymphatic sac was traumatized by the surgical procedure and/or affected by the toxicity of the infused drugs.

Selective lesioning of either cochlear or vestibular sensory cells cannot be created by the methods used in this experiment, whereas application of a gentamicin pledget[9] or streptomycin pellets[15] on the lateral membranous canal can selectively affect the vestibular labyrinth. In the present study, the nonselective type of lesion may be due to drug diffusion

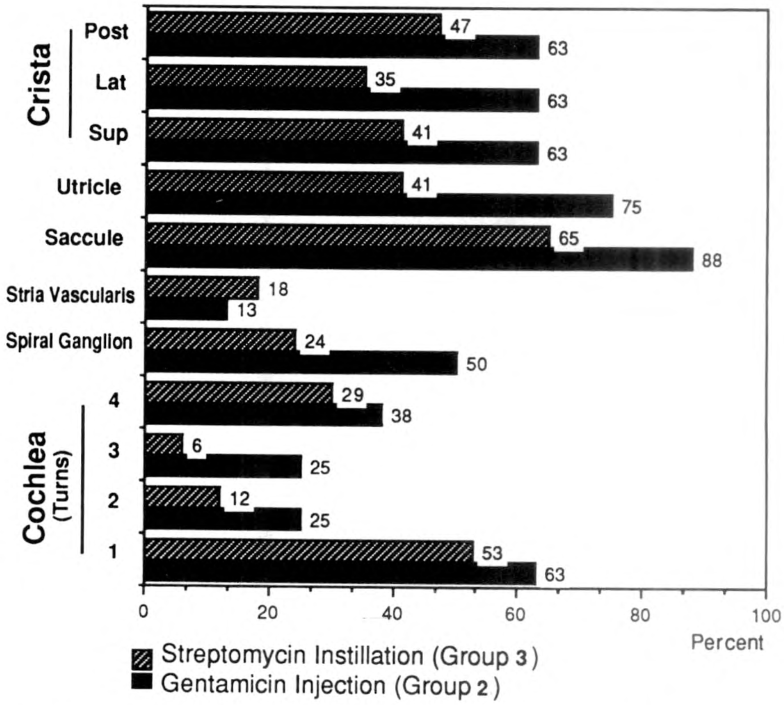

Fig 2. Sensory cell degeneration resulting from gentamicin injection versus streptomycin instillation.

through the endolymphatic space, in contrast to the lateral canal pledget technique, in which the perilymphatic trabecular meshwork and the membrana limitans are believed to be important in preventing or minimizing the spread of the drug toward the cochlea.

In the absence, or even in the presence, of longitudinal flow of endolymph, aminoglycosides can be transported from the instillation site, where their concentration is high, to other regions via passive diffusion and other mechanisms. The distance of the diffusion is dependent on the concentration of the drug and the endolymph flow rate. Several investigations have measured endolymphatic flow with different methods and the results have differed substantially. Giebel[16] used fluorescent tracers and estimated the rate of longitudinal flow to be 0.67 mm/min. Pröschel et al[17] used the threshold shift of the compound action potential after application of ototoxic drugs and estimated flow rates to be 3.7 and 0.5 mm/min in the first turn and second turn, respectively. Syková et al[18] measured flow using tetraethylammonium and determined the rate of endolymph flow to be 0.2 mm/min; the authors later corrected this figure to 0.1 mm/min.[19] In contrast to these relatively high longitudinal flow rates, Salt et al[20] found no significant volume flow in turn 1 (less than 0.01 mm/min) by measuring the activity of tetramethylammonium ion with ion-sensitive microelectrodes and concluded that the spread of the tracer was dominated by passive diffusion processes with very little contribution from longitudinal endolymph flow. Thalmann et al[21] hypothesized that the composition of endolymph might be maintained by the stria vascularis without major movement of water. Thus, the concept of longitudinal flow of endolymph is challenged by the proposal that there is virtually no endolymph movement toward the endolymphatic sac. Arnold et al[22] injected thorium dioxide into the endolymphatic sac of the guinea pig and found the tracer within the scala media 24 hours later. This finding was interpreted to mean that endolymph can move from the endolymphatic sac to the cochlea. Aminoglycosides are not ideal markers for the study of fluid transport. The extent of lesions depends on the rate of fluid turnover, cell sensitivity, and affinity for the drug at particular locations. The movement of an aminoglycoside from the endolymphatic sac to the cochlea and vestibular end organs through the narrow endolymphatic duct (30 μm in diameter in some parts) does not constitute proof against the existence of longitudinal endolymph flow or proof for the existence of reverse flow. However, this result casts some doubt on the existence of strong longitudinal flow toward the sac.

Passive instillation techniques cause less damage to cochlear sensory cells than drug injections. Gentamicin injections into the endolymphatic sac caused greater hair cell lesions than application of gentamicin on the opened sac (Nos. 1 and 7). Similarly, the injection of gentamicin into the lateral semicircular canal more frequently produced lesions in the cochlear sensory cells than application of gentamicin in the perilymphatic space of the same canal.[23] The passive application of streptomycin to the endolymphatic sac might be applicable for treatment of the vestibular symptoms in deaf patients with Meniere's disease solely or in conjunction with endolymphatic sac decompression. This procedure may aggravate endolymphatic hydrops, but the drug effect is clearly manifested on the sense organs, which are apparently the cause of the clinical symptoms. Perhaps other drugs that alter secretory activity can be substituted. Streptomycin instillation in the endolymphatic sac primarily affects the sensory cells of the macula sacculi, followed by those of the basal turn of the cochlea and the crista of the posterior ampulla. Further studies of controlled drug titrations are necessary to illuminate possible clinical applications of this technique.

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ABSCESSES OF THE NECK IN INFANTS AND YOUNG CHILDREN

A REVIEW OF 112 CASES

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A review of 112 patients 5 years of age and younger with cervical abscesses is reported. *Staphylococcus aureus* and group A β-hemolytic *Streptococcus* were cultured most often: in 39% and 17% of patients, respectively. Sixteen patients (14%) had unusual abscesses such as infected congenital cysts, cat-scratch disease, or mycobacterial abscesses. One patient had a necrotizing infection with group A streptococci and anaerobic streptococci. Intravenous antibiotic therapy was used in 104 patients, with 94% of these patients receiving a penicillin derivative, usually an antistaphylococcal penicillin. Ninety-six percent of the patients had incision and drainage of their abscesses; 8 patients required more than one incision and drainage. Two patients required airway intervention, 1 by intubation and 1 by tracheotomy. Most pediatric cervical abscesses respond well to appropriate intravenous antibiotic therapy and incision and drainage.

KEY WORDS — antibiotics, cervical abscess, incision and drainage, *Mycobacterium*, necrotizing fasciitis, *Staphylococcus*, *Streptococcus*.

INTRODUCTION

Abscess formation in the cervical area is a relatively common occurrence in young children. Abscesses involving only the neck and not involving peritonsillar, retropharyngeal, or parapharyngeal spaces have been common in our experience at the Los Angeles County–University of Southern California Medical Center. To evaluate the cause, bacteriology, and clinical courses of these abscesses, we reviewed our experience between January 1, 1982, and June 1, 1989, with abscesses of the neck in children 5 years of age and younger. Whereas cervical abscesses are relatively common in younger children, in our experience they have been an infrequent problem in children over the age of 5 years. This age distribution has also been mentioned in the literature.[1] For this reason, we decided to limit this review to children 5 years of age and younger. This review does not include patients with cervical adenitis or cellulitis who recovered with antibiotic therapy alone without surgical intervention. Only patients who underwent incision and drainage (I&D) or needle aspiration of pus are included.

In this paper, cervical abscess is defined as an inflammatory soft tissue swelling visible and palpable in the neck and containing a localized collection of purulent material. Abscesses of the fascial spaces adjacent to the pharynx are not included in this series with the exception of one patient in whom a retropharyngeal abscess was associated with a cervical abscess.

PATIENTS AND METHODS

During the $7^1/_2$-year period of this review, 112 patients fulfilled the criteria, as stated in the Introduction, for inclusion in the study. The ages of the 112 patients were as follows: under 12 months, 51 (46%); 1 year, 28 (25%); 2 years, 13 (12%); 3 years, 11 (10%); 4 years, 5 (4%); and 5 years, 4 (3%). Almost one half of the patients were under 12 months of age, and 93% were under 4 years. The age period of 6 to 12 months had the highest number of cases of any 6-month period (34). Seventeen patients were under 6 months of age and 8 were under 3 months; the youngest patient was 22 days old on admission. Eighty-four percent were Hispanic, 6% were white, 5% were black, and 5% were Asian. Sixty-four (57%) of the patients were female; 48 were male.

Abscess Location and Characteristics. Ninety-three percent of the abscesses were in the lateral neck. Eighty-seven percent were in the anterior triangle, although the swelling with some of the larger ones extended into the posterior triangle also. All of the lateral cervical anterior triangle abscesses were high in the neck, in the submandibular space or at the angle of the mandible. Four patients had bilateral abscesses. Those abscesses in the posterior triangle were evenly divided between high and low locations. Seven percent of the abscesses were in the midline anteriorly. Most were in the submental or hyoid area, but two were low in the neck. None of the submental abscesses involved swelling of the floor of the mouth. Of the abscesses located in the lateral neck, twice as many were on the left side as were on the right side. The abscesses varied in size from 2 to 10 cm in diameter. Except in submandibular and submental abscesses, it was impossible to describe the abscesses as occupying a particular fascial space. Only 52% were definitely fluctuant at the time of drainage (see Figure, A). Many of the

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Presented at the 73rd meeting of the Pacific Coast Oto-Ophthalmological Society, Kauai, Hawaii, June 28, 1989.

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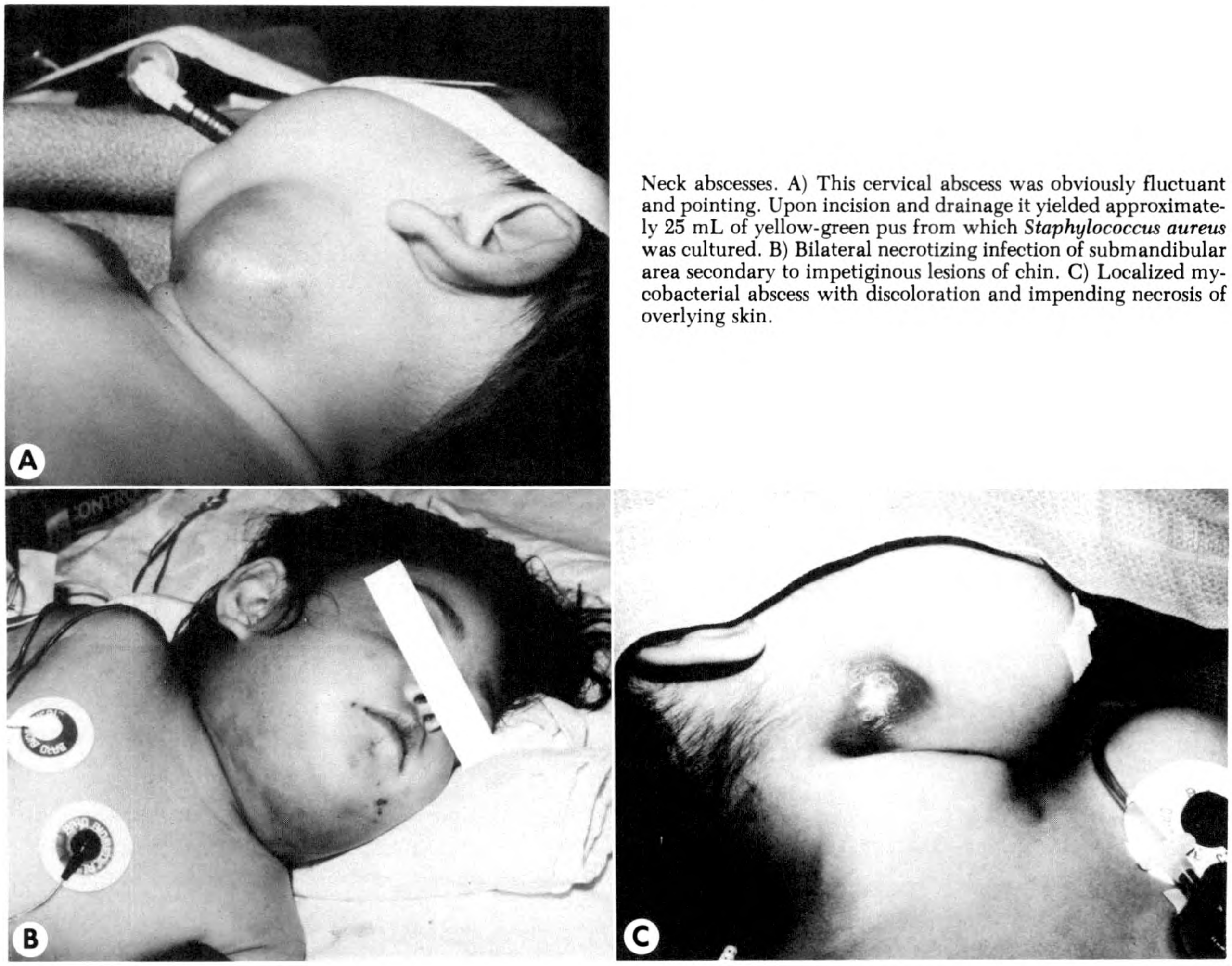

Neck abscesses. A) This cervical abscess was obviously fluctuant and pointing. Upon incision and drainage it yielded approximately 25 mL of yellow-green pus from which *Staphylococcus aureus* was cultured. B) Bilateral necrotizing infection of submandibular area secondary to impetiginous lesions of chin. C) Localized mycobacterial abscess with discoloration and impending necrosis of overlying skin.

deeper abscesses were considered to have a feeling to palpation of "probable fluctuance." Most were tender to palpation. The maximum temperature varied widely, with 5% of patients having temperature below 37°C and 11% with fever over 40°C.

Laboratory and Radiographic Data. Fifty-seven percent of the patients had white blood cell counts of between 10,000 and 20,000, 34% had counts of over 20,000, and 7% had counts of over 30,000. Approximately one fourth of the patients had hemoglobin levels of less than 10 g. Most of the patients had chest and neck radiographs, but only a few had either ultrasonography or computed tomographic scans; these were reserved for patients in whom either the presence or the location of an abscess was in doubt. In the majority of our patients, this presence or absence was determined by physical examination alone. Tuberculin skin tests were performed on almost all of the patients.

Types of Abscesses. In the 112 patients, 107 abscesses developed in areas of cervical adenitis. Five abscesses developed in previously undiagnosed congenital cysts; 3 were thyroglossal duct cysts, and 2 were lateral neck cysts. Of the lateral cysts, 1 was of branchial cleft origin, and the other was of unknown type.

Ninety-one of the 107 abscesses developing from cervical adenitis were what we classified as "regular" abscesses, meaning that they were unilateral abscesses that responded to drainage and appropriate antibiotic therapy. Sixteen others are classified as "unusual" regarding cause, presentation, or management. Eight of the 16 were of atypical mycobacterial causation. All 8 patients had positive tuberculin skin test reactions, while all of the other patients tested had negative reactions. Four other cases were classified as unusual because they were bilateral. In 2 other patients, cat-scratch disease was the cause of their abscesses. One 9-month-old patient had a retropharyngeal abscess in addition to a cervical abscess and required intubation for airway obstruction. One 2-year-old patient had a tracheotomy because of the large size of the cervical abscess with pharyngeal edema.

Source of Abscesses. The exact source of infection that led to abscess formation was unknown in most of the patients. In the 5 with infected cysts, the cyst itself was the site. Of those with adenitis abscesses, the source of origin was thought to be infected skin sores in 4, insect bites in 3, infected pierced earlobe

TABLE 1. ANTIBIOTICS ADMINISTERED

Antibiotic	*No. of Patients*
Oxacillin sodium alone	29
Oxacillin sodium in combination	33
Methicillin sodium alone	10
Methicillin sodium in combination	10
Penicillin G potassium in combination	19
Ampicillin sodium in combination	13
Cefuroxime sodium alone	6
Cefuroxime sodium in combination	11
Other combinations	8

in 1, infected trauma site in 1, and dental infection in 1. Seventy-four other patients had upper respiratory tract infections, some with otitis media and/or pharyngitis, which were suspected of playing an etiologic role in their abscesses.

Antibiotic Therapy. Three patients were managed with oral antibiotic therapy as outpatients. These included 1 with regular adenitis abscess, 1 with mycobacterial abscess, and 1 with thyroglossal duct cyst abscess. The other 109 patients were hospitalized for periods ranging from 3 to 28 days. The average period of hospitalization was 7 days. All hospitalized patients except those thought to have mycobacterial abscesses received intravenous antibiotic therapy (Table 1).

Drainage of Abscesses. Four patients had only needle aspiration of their abscesses. These included 1 patient with a thyroglossal cyst abscess, 1 with a mycobacterial abscess, 1 with a regular adenitis abscess, and 1 with a branchial cleft cyst. The other 108 patients underwent I&D of their abscesses, although some had one or more needle aspirations before the I&D. Eighty-two percent of the I&D procedures were performed in treatment rooms under sedation and local anesthesia. Eighteen percent were performed in the operating room under general anesthesia, either endotracheal or with intravenous ketamine hydrochloride and mask ventilation. In general, the deeper abscesses and the mycobacterial abscesses were drained under general anesthesia.

RESULTS

Culture Results. Aerobic cultures were taken from every abscess and anaerobic cultures were also taken in most instances. Mycobacterial cultures were obtained only in those patients with a positive tuberculin skin test and history or physical findings suspicious for a mycobacterial infection. All cultures were Gram-stained. Aerobic cultures were plated on blood agar, MacConkey agar, phenylethyl alcohol agar, thioglycolate broth, and laked kanamycin vancomycin agar. Anaerobic cultures were plated on *Brucella* medadione blood agar and *Bacteroides* bile esculin agar. Sensitivity tests were performed on all positive cultures. Mycobacteria were cultured with a modified Petroff method. The culture results are shown in Table 2.

TABLE 2. RESULTS OF ABSCESS CULTURE

Bacteria	*No. of Patients*
Staphylococcus aureus alone	44
Staphylococcus aureus in combination	3
Group A β-hemolytic *Streptococcus*	15
Group A *Streptococcus* in combination	4
Atypical mycobacteria	
Mycobacterium avium	5
Mycobacterium intracellulare	2
Unidentified	1
Anaerobic bacteria	
Anaerobic *Streptococcus*	1
Microaerophilic *Streptococcus*	1
Peptostreptococcus	1
Hemophilus influenzae, not type B	1
Various others cultured in combination with above	7
No growth	29

Of the 4 patients with bilateral abscesses, 3 yielded *Staphylococcus aureus*. The fourth patient had a necrotizing bilateral submandibular infection (see Figure, B) that grew group A β-hemolytic *Streptococcus* and anaerobic *Streptococcus*. Of the 5 with infected cysts, only 1 had a positive culture. This patient had an infected thyroglossal duct cyst that cultured *Eikenella corrodens* and microaerophilic *Streptococcus*. There was no correlation between the site of the abscess or the suspected source and the culture results.

Blood cultures were performed on 59 patients, usually limited to those with fevers above 38°C, and were positive in only five instances. Group A β-hemolytic streptococci were cultured twice, *S aureus* once, *Neisseria sicca* once, and α-hemolytic streptococci once. The *S aureus* blood culture and one of the two positive for group A streptococci were in patients who also had abscess cultures positive for the same organisms.

Courses After Incision and Drainage. Drains were removed from the "regular" abscesses after 2 to 3 days and after 1 day in the mycobacterial abscesses. The duration of intravenous antibiotic therapy averaged 3 days after I&D, followed by an oral antibiotic for approximately 1 week. Ten patients had to have their I&D repeated. In 8 patients, it was repeated once. These repetitions of I&D were due to persistent deep loculations of the abscess or multiple fluctuant sites. In 2 other patients, more than one repeat I&D was necessary. One of the 2 patients was found to have cat-scratch disease upon pathologic examination of the abscessed node that was excised after two I&D procedures had been unsuccessful in alleviating the infection. The second patient was a 3-year-old girl (see Figure, B), referred to earlier in this paper, who had a bilateral submandibular necrotizing infection secondary to an impetiginous lesion on her chin that was complicated by septic hypotension and disseminated intravascular coagulation. The initial I&D was through a wide incision on the left side that drained both sides. The purulent collections resolved initially but then re-formed. She required four subsequent drainage and debridement procedures.

The 8 patients with mycobacterial abscesses were under treatment by the pediatric pulmonology service with antituberculosis medication, usually isoniazid, rifampin and pyrazinamide, or ethambutal hydrochloride. The lesions continued to progress, became fluctuant, and developed changes in the overlying skin (see Figure, C). Atypical mycobacterial causation was suspected, but was not proven until culture results were obtained from needle aspiration or the I&D specimen. When these culture results indicated an atypical organism resistant to chemotherapy, the medications were discontinued. These 8 patients, who accounted for most of the patients in this review with courses of over 3 weeks' duration, were improved after removal of purulent and caseous material from the abscesses.

The patient with the retropharyngeal and cervical abscesses who was intubated was able to be extubated 12 hours after drainage of both abscesses. The 1 patient who had a tracheotomy required a second I&D of her large abscess 36 hours after the first I&D. Her tracheotomy was removed 3 days later. Of the 5 patients who had abscesses in congenital cysts, the capsule of the cyst of unknown type was excised during the I&D procedure. The other 4 patients had electively scheduled excisions of the cysts after the infections had subsided. There were no fatalities.

DISCUSSION

Cervical abscesses as defined in this paper are most common in the 6- to 12-month age group, and the frequency decreases with increasing age through 5 years, after which they are very infrequent. Ninety-five percent of our patients were febrile and 91% had an elevated white blood cell count. The degree of elevation of temperature or of white blood cell count could not be correlated with age of the patients or the bacterial causation of the abscesses. Girls outnumbered boys 57% to 43%, and for some reason, twice as many abscesses occurred on the left side of the neck as on the right.

Except for the common association of an upper respiratory tract infection, the source of infection was often obscure in our patients. This is consistent with recent reports by Dodds and Maniglia[2] and Brook,[3] who report on a broader range of pediatric ages. In the report of Dodds and Maniglia,[2] no patients younger than 5 years had dental sources, and only 1 of our patients had a dental infection. In Brook's series,[3] 3 of 36 patients had infected congenital cysts, whereas 5 of our 112 patients did. More of his patients had traumatic (19%) and dental (23%) sources than ours did, but the mean age of his series was 9 years. In an earlier study, Adekeye et al[1] reported on 81 patients in East Africa with a mean age of 4 years. They found an increase in the amount of anemia present, with 62% of their patients having a hemoglobin level less than 11 g, while we found that 25% of our patients had a level less than 10 g. They postulated that the presence of malnutrition in a large part of their population might contribute to the increased susceptibility to pyogenic infections in those children. Our patients, most of whom are indigent, typically rely on an unbalanced diet and might also be predisposed to an increased susceptibility to infections.

Staphylococcus aureus and group A β-hemolytic *Streptococcus* were the most frequently isolated organisms in our patients as well as in patients in earlier reports.[1-5] The low incidence of anaerobic bacteria is consistent with the report by Brook[3] that these organisms are recovered more frequently in abscesses of the head than of the neck. Anaerobic bacteria are also more often cultured from abscesses of dental origin[3,4] — an almost negligible source in our series. *Hemophilus influenzae*, so often involved in ear and sinus infections and implicated in chronic tonsillar hypertrophy,[6] was cultured only once.

Brook's[3] statement about increased virulence of combined aerobic and anaerobic infections is supported by our experience with the patient with the necrotizing infection due to group A β-hemolytic streptococci and anaerobic streptococci. This type of infection has been referred to under several names such as necrotizing fasciitis, synergistic necrotizing cellulitis, etc, as listed by Beck et al.[7]

The eight mycobacterial abscesses were a small portion of a larger series of patients with mycobacterial cervical adenitis managed at the Los Angeles County–University of Southern California Medical Center. Lack of response to appropriate chemotherapy with progression of fluctuance and impending skin breakdown made surgical intervention necessary. Our policy usually is to try needle aspiration initially. If aspiration is not effective and it is possible to excise the entire abscessed nodes, we do so. Often close proximity to the ramus mandibularis of the facial nerve and/or a large area of involved skin make total excision impractical. In these cases, the purulent and caseous material is removed from the abscess by suction and curettage through an incision in normal skin about 1 cm below the abscess. We feel that the appropriate therapy for most atypical mycobacterial lymphadenitis is surgical, with chemotherapy more effective for *Mycobacterium tuberculosis* infections. This is in agreement with the current literature.[8,9]

Since *S aureus* and group A β-hemolytic *Streptococcus* are the most common pathogens in cervical abscesses in young children, an antistaphylococcal penicillin such as oxacillin or methicillin seems to be the logical first-line antibiotic for treatment. If anaerobic involvement is suspected, an antibiotic effective against anaerobes should be added. Since *H influenzae* is a rare pathogen in cervical abscesses, antibiotic coverage for this organism is not necessary in the usual cases. We feel that children with cervical abscesses other than of mycobacterial origin should receive intravenous antibiotic therapy. Adequate antibiotic blood levels for abscess treatment simply cannot be obtained with oral therapy.

Surgical I&D under local or general anesthesia is the most effective treatment and provides the shortest course of hospitalization. Although the possibility of airway obstruction should always be considered, this was a rare occurrence in our series of patients, with only 2 requiring airway management.

CONCLUSION

Abscesses of the neck are relatively common in young children, especially those 6 to 12 months of age. The usual workup should include accurate history and physical examination, complete blood count, chest x-ray study, and blood culture if pyrexia is present. Computed tomography or ultrasound should be used only in selected patients, as stated earlier in the text. Abscesses usually arise in an area of cervical adenitis, and the bacterial pathogens are most often *S aureus* or group A β-hemolytic *Streptococcus*. These usually respond well to intravenous therapy with an antistaphylococcal penicillin and I&D of the abscesses.

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Ann Otol Rhinol Laryngol 100:1991

IN VITRO CILIOGENESIS IN RESPIRATORY EPITHELIUM OF CYSTIC FIBROSIS PATIENTS

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Nasal epithelial cells, dissociated from nasal polyps of three cystic fibrosis patients, were cultured on collagen gels until all cilia were lost, and then the cells were released in suspension as cell sheaths to form aggregates and vesicles. Cilia reappeared after 1 week. The number of ciliated cells increased progressively and within 1 month large areas of the aggregates were ciliated. These newly formed cilia were ultrastructurally normal. The ciliary activity was well coordinated and resulted in continuous movements of the aggregates in the culture medium. In the supranuclear cytoplasm the different ciliogenetic precursors were found: fibrogranular aggregates with occasionally small tubules, deuterosomes with procentrioles, kinetosomes, basal bodies, and short cilia. Initial stages of ciliary shaft formation, such as elevation of the apical membrane above the basal bodies without axonemal ultrastructure, could be well documented. The results indicate that in cystic fibrosis, ciliogenesis and the resulting ciliary activity in vitro are indistinguishable from those seen in cells from control tissue.

KEY WORDS — cell culture, ciliary beating, ciliogenesis, cystic fibrosis.

INTRODUCTION

One of the major problems in cystic fibrosis, the most frequent lethal autosomal-recessive inherited disease of the white race, is the impaired mucociliary transport over the respiratory tract. This transport depends on the composition of the electrolyte solution and mucins and on effective and coordinated ciliary beating. The defective cyclic adenosine monophosphate–mediated activation of chloride channels in the apical membrane of respiratory epithelial cells[1,2] diminishes chloride secretion.[3,4] This effect, in combination with an increased Na^+ resorption,[5] likely causes dehydration of the respiratory mucus and depletion of the periciliary fluid. Alterations in composition of the mucins are reported, but their relevance is not yet known. Reproducible and reliable methods for both in vivo and in vitro studies of electrolyte transport and of mucin secretion and composition exist, but one can study ciliary structure only in biopsies, and ciliary activity only by measuring transport velocity in vivo and ciliary beat frequency in biopsies.

In cystic fibrosis patients, ciliary beat frequency is reported to be normal, but mucociliary transport is frequently impaired,[6,7] and ultrastructural alterations are found.[7-9] However, these alterations are not always present[6] and could be secondary to infection or inflammation.[7-9] Indeed, the respiratory tract of cystic fibrosis patients is frequently colonized by *Pseudomonas aeruginosa* species and other bacteria that produce ciliotoxic agents.[10] This rather specific bacterial colonization interferes not only with in vivo but also with in vitro studies of ciliary activity. Therefore, the intrinsic ciliary activity of respiratory epithelial cells in cystic fibrosis must be studied in a reproducible culture system in which the cilia have not been exposed to ciliotoxic agents. The reasons for the frequent and almost specific colonization of the respiratory tract with *P aeruginosa* and *Staphylococcus aureus* in cystic fibrosis are not known. To study the role of the apical membrane in the adherence and colonization by these bacteria and to determine whether some specific inherited membrane characteristic is present in cystic fibrosis that might enhance this colonization, the availability of an in vitro culture system with ciliated apical membranes and related cell organelles is essential. Once again, these apical membranes must be "clean" to exclude secondary effects.

In previous studies, we demonstrated that in a suspension culture system in vitro ciliogenesis occurs[11] and results in normal and coordinated ciliary beating.[12] We also showed for the first time in human cells in an vitro culture system the presence of different cytoplasmic ciliogenetic precursors and proposed the following sequence of events in ciliogenesis: appearance of long microvilli, various forms of fibrogranular aggregates with eventually small tubules, deuterosomes with procentrioles, kinetosomes, aligned basal bodies, and short cilia.[13] This sequence of events agrees well with the observations made during mammalian embryogenesis.[14-16] Here we extend these observations to cystic fibrosis and show that ciliogenesis in cystic fibrosis nasal epithelial cells is possible and indistinguishable from that seen in cells from control tissue.

MATERIALS AND METHODS

Cell Culture. The methods of cell isolation and

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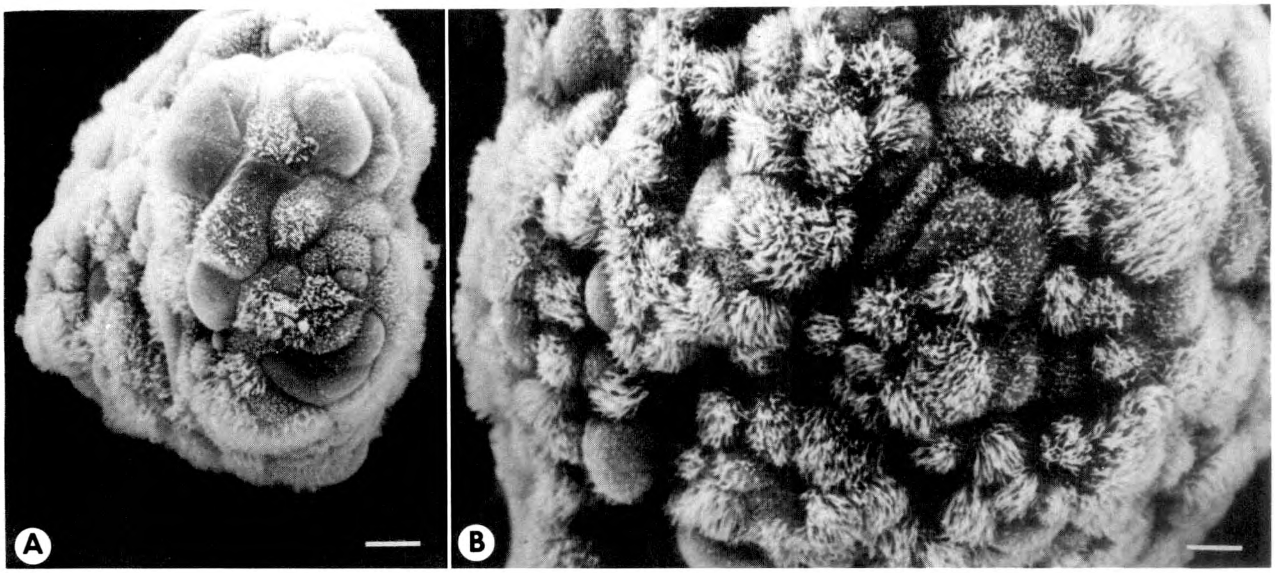


Fig 1. Aggregates of nasal epithelial cells from cystic fibrosis patients during ciliogenesis. Bars — 10 µm. A) After 2 weeks some cells have normal cilia, while on other cells limited number of short cilia are present. B) After 3 weeks whole areas of aggregates are covered with a ciliary tapestry.

cell culture have been described extensively in previous papers.[11,12] Briefly, nasal polyps from three cystic fibrosis patients were repeatedly washed in Ham's F-12 Dulbecco's modified Eagle's medium 1/1 (Gibco) supplemented with penicillin (50 IU/mL) and streptomycin (50 µg/mL) to eliminate the mucus and to reduce maximally the inevitable bacterial contamination. The polyps were then digested with 0.1% pronase (Sigma) in the same medium at 4°C overnight. After three washes in culture medium, the dissociated epithelial cells were preplated for 1 hour on plastic to reduce the number of contaminating fibroblasts and then plated on a rat tail collagen gel at a density of less than 1,000 cells/cm^2 in T75 flasks (Falcon) containing 15 mL of medium and cultured at 37°C in a 5% carbon dioxide atmosphere. The culture medium consisted of Ham's F-12 Dulbecco's modified Eagle's medium 1/1 supplemented with antibiotics, cholera toxin (10 ng/mL; Sigma), retinoic acid (10^{-7} mol/L; Sigma), and 2% Ultroser G (Gibco), and was changed after 1 day and from then on three times a week. After 2 weeks the monolayers reached confluency and the cell number increased at least fiftyfold. Within 4 weeks all cilia had disappeared from the monolayer-cultured cells. To transfer these deciliated cell sheaths to the suspension culture system, collagenase type II (200 IU/mL; Worthington Biochemical Corp) was added. Hundreds of epithelial aggregates and vesicles were formed during the first week on a gyratory shaker at 80 rpm. The culture medium, with 10% NU-serum (Flow Laboratories) instead of the 2% Ultroser G, was changed after 1 day and from then on three times a week. T25 flasks (Falcon) containing 7 mL of medium were used for the suspension cultures. Similar investigations were previously done on cells from control tissues (n = 15) under identical conditions (unpublished observations).

Scanning Electron Microscopy. Aggregates and vesicles from the three patients were fixed in glutaraldehyde 3% (Fluka) in 0.1 mol/L sodium cacodylate buffer (pH 7.4) for 2 hours. The dehydration in a graded ethanol series was completed by a critical point drying (E300-Polaron) with carbon dioxide. The mounted specimens were sputter-coated with gold (E5100-Polaron) and viewed in a PSEM 500 electron microscope (Philips).

Transmission Electron Microscopy. Fixation of aggregates and vesicles from two patients in glutaraldehyde 3% in sodium cacodylate buffer was followed by postfixation in osmium tetroxide 1% in 0.1 mol/L phosphate buffer (pH 7.4) for 1 hour. The dehydrated material was embedded in Epon 812, cut on an LKB ultramicrotome, and finally stained with uranyl acetate and lead citrate for viewing in a Philips 201 electron microscope.

Evaluation of Ciliary Function. Qualitative evaluation of the ciliary activity was done under phase-contrast microscopy. Specifically, the temperature sensitivity of ciliary beat frequency was used to distinguish at 5°C the slow recovery phase and the fast effective phase. In addition, interciliary coordination and the presence of a metachronal waveform were looked for. At 37°C the percentage of aggregates moving continuously and the 360° rotation time of the "fastest" aggregates were measured. Quantitative measurements of ciliary beating were not performed.

RESULTS

In the monolayer cultures from two patients

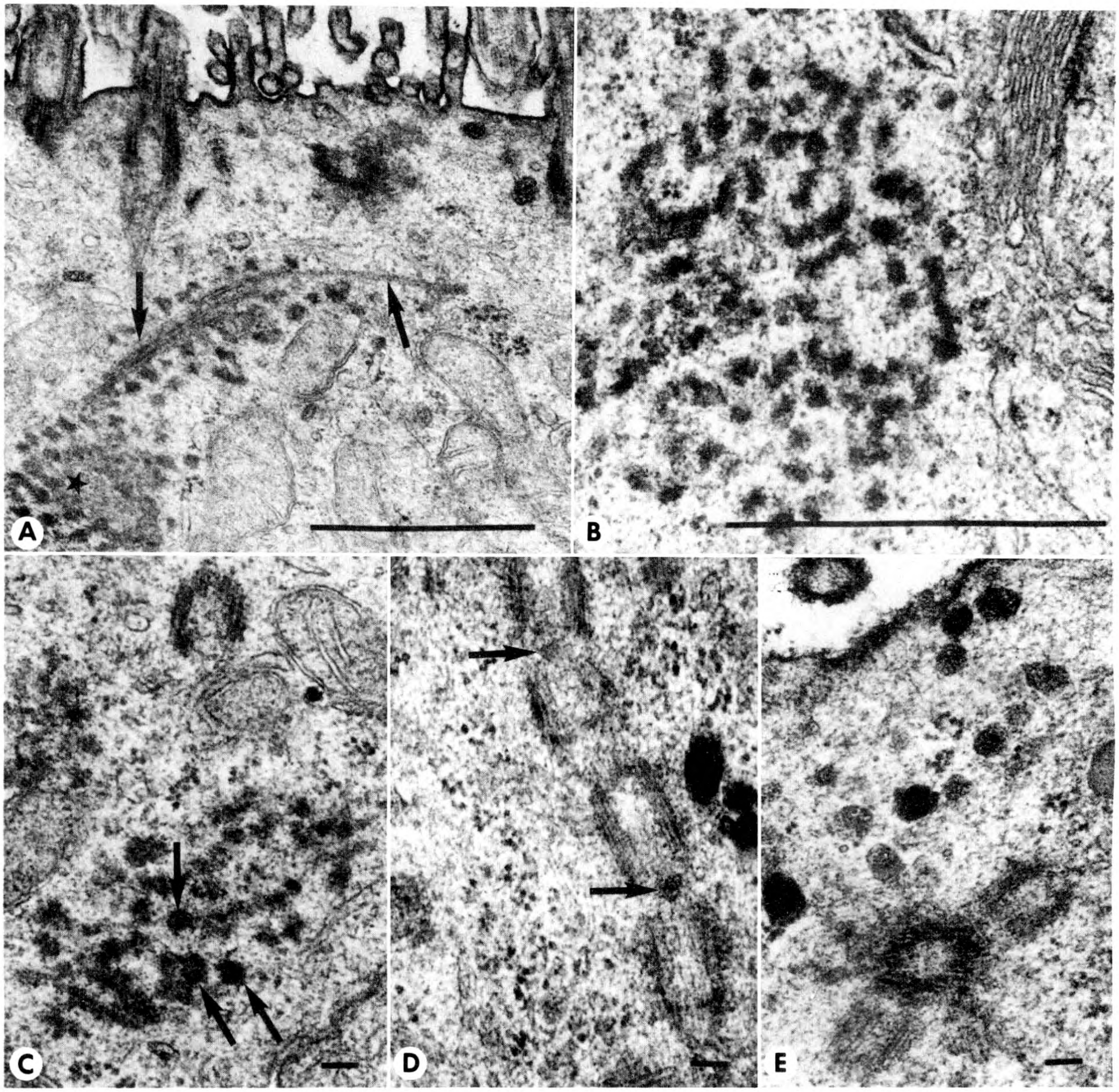


Fig 2. Ultrastructural characteristics of ciliogenetic precursor structures in cystic fibrosis. A) Microtubules (arrows) run through fibrogranular aggregate with central fibrous area of intermediate electron density (star). Bar — 1 μm. B) Granular part can be organized in ring or beads-on-a-string pattern. Bar — 1 μm. C) Small rings (arrows) are transverse sections of tubules and are found between granular elements. Bar — 0.1 μm. D) Two procentrioles located on deuterosomes (arrows). Bar — 0.1 μm. E) Several procentrioles are clustered in radial pattern. Bar — 0.1 μm.

there was no bacterial infection observed, but in 2 of the 20 T75 flasks of the third patient, infection became apparent after 10 to 14 days of monolayer culture. These infections were caused by a nonidentified *Pseudomonas* species, as could be expected from respiratory tract epithelium of cystic fibrosis patients.

After transfer to the suspension culture system, the deciliated nasal epithelial cell sheaths formed aggregates and vesicles as previously described for cultures from control tissues.[11] Microvilli and a glycocalyx coat were abundantly present on the apical membranes after a few days. Several hundreds of aggregates could be examined for each of the three patients.

In the first week, no or only a few cilia were observed. The number of ciliated cells increased progressively. After 2 weeks in suspension more than 10% of the cells were already ciliated (Fig 1A), and 1 week later whole areas of the aggregates and vesicles were ciliated (Fig 1B). After 1 month, 50% to 100% of the aggregated cells were ciliated. During the first weeks, very small buddings with the diameter of cilia were present on the apical membranes of some cells, while other cells had a limited number of short cilia. Various combinations of the number of cilia per cell (up to 250) and of the ciliary length (up to 7 μm) were found. Finally, the ciliated

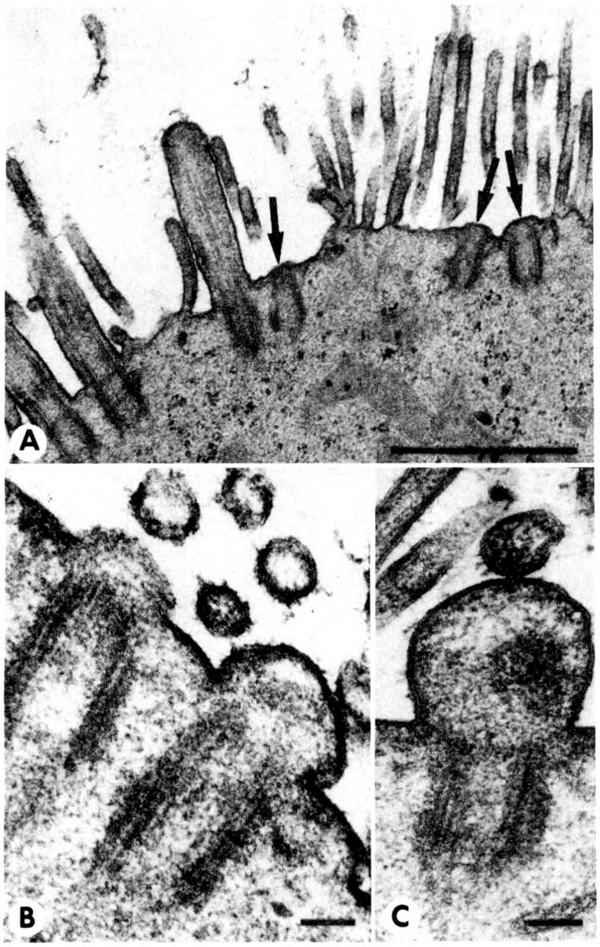
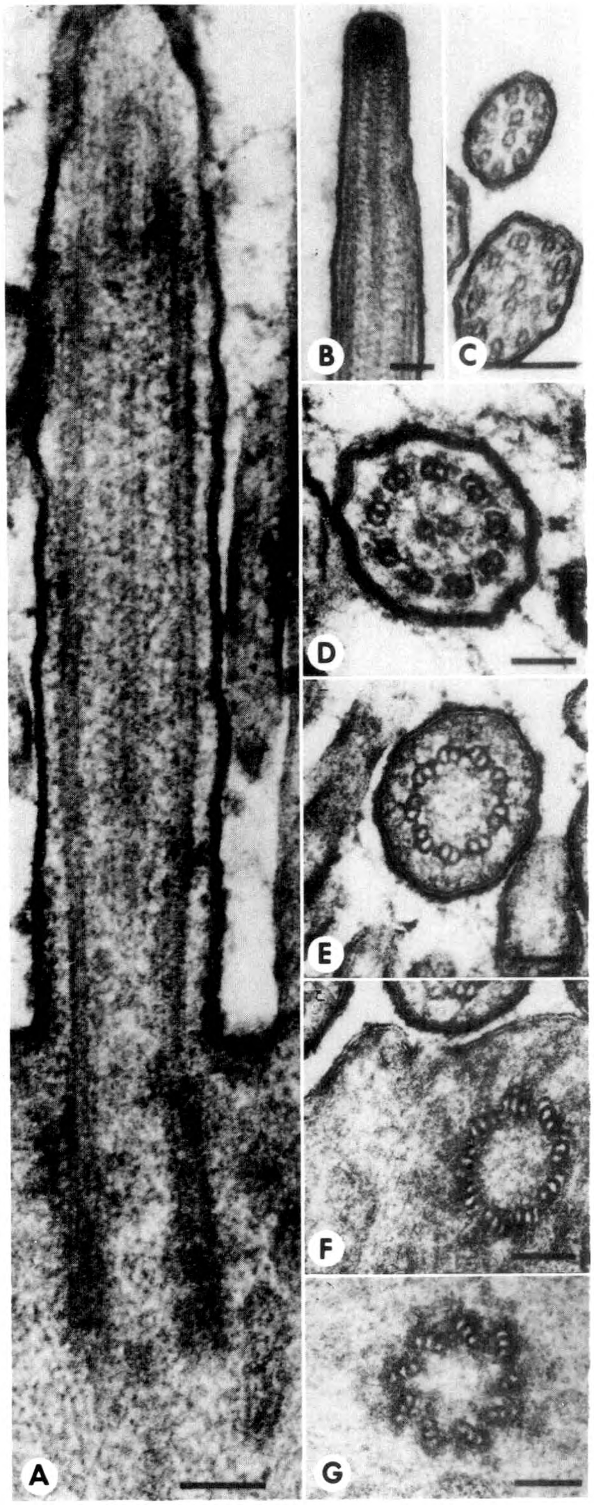


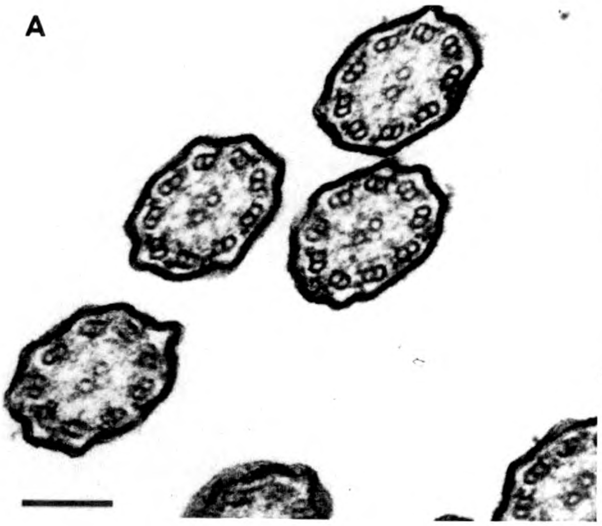
Fig 3. Initial stages of ciliary shaft formation in cystic fibrosis. A) Apical membrane overlying three aligned basal bodies is slightly elevated (arrows), while short cilium with axonemal ultrastructure is present on another basal body. Bar — 1 μm. B) Apical membrane above two basal bodies is more elevated. Bar — 0.1 μm. C) Basal body oriented perpendicular to surface is surmounted by budlike extension without recognizable axonemal organization. Bar — 0.1 μm.

cell contained more than 100 mature, 6- to 7-μm-long cilia.

The different forms of fibrogranular aggregates were frequently observed (Fig 2), including the rather aspecific granular complexes, the central areas of intermediate density (Fig 2A), the organization of granules in rings or a formation like beads on a string (Fig 2B), and the presence of microtubules running through the fibrogranular aggregates (Fig 2A). Very small tubular elements could be identified (Fig 2C), as well as procentrioles in clusters around a deuterosome (Fig 2D,E). Free, individual kinetosomes were located near the apical membrane. Basal bodies aligned with their longitudinal axis perpendicular to the apical membrane and overlying elevations of the apical membrane were observed (Fig 3A). We also found clearly bud-

Fig 4. A,B) Sagittal sections of cilium with C-G) corresponding transverse sections at different levels in cystic fibrosis. Bars — 0.1 μm. A) In this sagittal section specific elements of basal body and of lower part of cilium are recognized. B) Near tip, some diameter of cilium diminishes, but central pair of microtubules remains present. C) Near tip, some microtubules of nine doublets end, resulting in singlets and reduced number of doublets. In tip, central pair is surrounded by nine single microtubules. D) In ciliary shaft, complete axonemal structure is seen. E) Just above footplate, nine doublets are seen connected to ciliary membrane. F) In upper part of basal body, nine triplets are present at reduced angle toward tangent. G) In lower part, this angle increases to 40°.





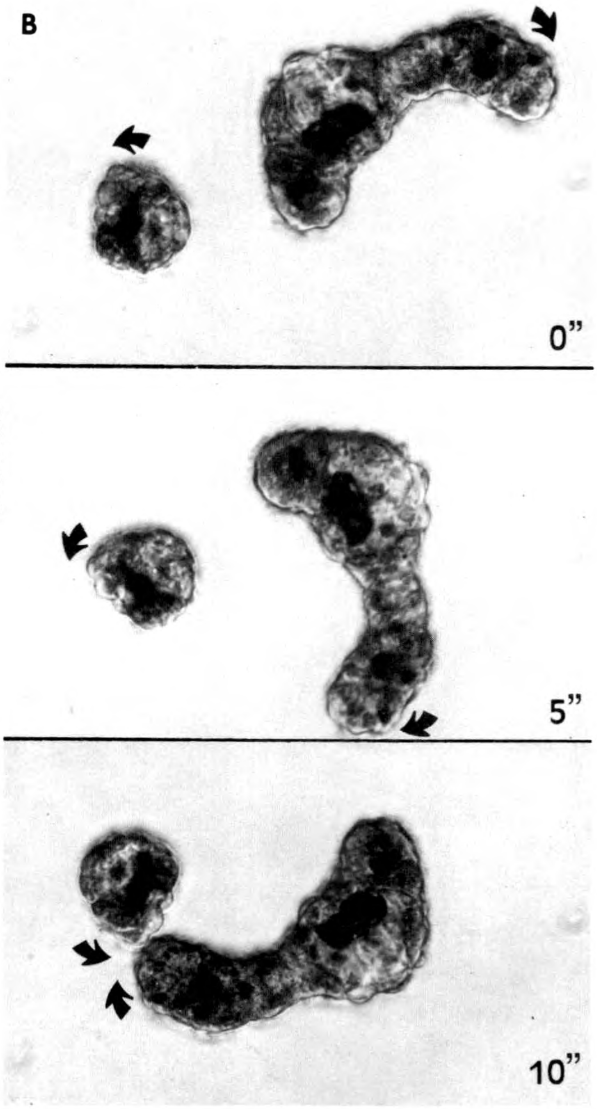


Fig 5. Structural and functional coordination of cilia in cystic fibrosis. A) Orientation of central microtubular pair varies only slightly, as is seen with transmission electron microscopy, which illustrates common orientation of cilia. Bar — 0.1 μm. B) Phase-contrast microscopic pictures taken at 5-second time intervals illustrate continuous movement of aggregates after 4 months in suspension culture, indicating functional (inter)cellular ciliary coordination. Arrows indicate direction of rotation: clockwise for larger aggregate and counterclockwise for smaller aggregate. Smaller aggregate measures approximately 50 μm in diameter.

like extensions of the apical membrane above a basal body without a recognizable axonemal ultrastructure (Fig 3B,C). This axonemal ultrastructure was present in short cilia (Fig 3A).

These cilia that developed in vitro in cells from cystic fibrosis patients (Fig 4) were identical to those of control cultures.[11,12] The basal bodies consisted of nine microtubular triplets at an angle of 40° to the tangent on the circle (Fig 4G), with basal feet extending laterally and rootlets pointing toward the cytoplasm. Higher up, the orientation of the triplets became parallel with the tangent on the circle (Fig 4F). Above the footplate, the nine triplets of microtubules changed into doublets, and these were linked to the shaft membrane and to the neighboring doublets (Fig 4E). The central pair of microtubules started higher. The ciliary membrane surrounded nine microtubular doublets with dynein arms toward one neighboring doublet and radial spokes to the central sheath around the central pair of microtubules (Fig 4D). Near the ciliary tip, the ciliary diameter decreased (Fig 4B) and one microtubule of the peripheral doublets ended, so that variable numbers of doublets and singlets were present (Fig 4C). In the tip, the remaining nine single microtubules surrounded the central microtubular pair (Fig 4C). Since the interciliary variation of the axis of the central pair of microtubules was very low (Fig 5A), the alignment of these newly formed cilia was completely normal.

After 2 to 3 weeks, continuous movements and rotations of the epithelial aggregates and vesicles were observed on the bottom of the culture flasks (Fig 5B). On phase-contrast microscopy, a fast flickering was seen at the borders of the aggregates at room temperature. At lower temperatures, the characteristic beat pattern with both fast (effective) and slow (recovery) phases was recognized in the individual cilia. Cilia on the same cell and even on neighboring cells beat in the same direction and in phase. A metachronal waveform was also present. More than 90% of the aggregates from cystic fibrosis patients as well as those from control tissue showed continuous movements after 1 month. The "most active" aggregates from cystic fibrosis patients rotated 360° in less than 20 seconds; this rate is similar to that seen in cells from control tissue. These reciliated epithelial vesicles and aggregates remained in culture for more than 5 months, and even after that time the continuous movements and rotations of the aggregates and vesicles were maintained.

DISCUSSION

The present report describes in vitro ciliogenesis of respiratory epithelium from patients with an inherited disease affecting mucociliary transport: cystic fibrosis. The first problem in studying ciliary activity in cystic fibrosis is the inevitable colonization and infection by bacteria such as *Pseudomonas*. Although infection does occur in this system, it is not limiting, and a sufficient number of cells can be cultured properly to investigate ciliary activity in vitro. The second problem in studying cystic fibrosis in vivo is the continuous exposure of cilia to various environmental products and toxins. When the cells from cystic fibrosis nasal polyps are placed in suspension cultures, most cells are newly formed unciliated cells resulting from cell divisions in the monolayer cultures. The few remaining cells from the original polyps have lost all their cilia. Therefore, the cilia formed during the suspension culture are new cilia and thus have only been exposed to the defined culture medium.

The polarization of the cells in the aggregates and vesicles with abundant microvilli apically and a glycocalyx coat shows that these cells express many differentiated characteristics of respiratory epithelial cells. The progressive reappearance of ciliated cells, starting the first week of suspension culture and progressing further over 1 month, is indistinguishable from that of control cultures.[11]

The normal structure and function of these cilia is shown by their diameter, length, axonemal and basal body structure, and characteristic beating pattern and the continuous movement of the epithelial aggregates and vesicles.[12] However, functional evaluation was only qualitative, since no quantitative analysis of ciliary beat cycle and coordination was performed. Moreover, the multiple cytoplasmic precursor structures for basal body formation demonstrate that the process of ciliogenesis itself in cystic fibrosis is comparable to that in cells from control tissue[13] and in mammalian embryogenesis.[14-16]

All these observations clearly show that in vitro ciliogenesis in cystic fibrosis cannot be distinguished from that in cells from control tissue. Moreover, the abnormalities seen in biopsies of nasal mucosa from some cystic fibrosis patients[8,9] could not be observed.

This system provides us with the possibility for long-term study of ciliary activity itself and of the influences of various environmental factors such as bacteria and their toxins on the respiratory epithelium of cystic fibrosis patients. Unless the population of cystic fibrosis cells studied here is not representative of the in vivo population, one can conclude that these results support earlier observations[6] and suggest that the abnormalities of cilia in vivo reported by some investigations[8,9] are not primary defects intrinsic to the cilia, but must be consequences of environmental factors such as infection.

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KERATINS AS MOLECULAR MARKERS OF EPITHELIAL DIFFERENTIATION: DIFFERENTIAL EXPRESSION IN CRYPT EPITHELIUM OF HUMAN PALATINE TONSILS

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The expression of keratins in the stratified squamous nonkeratinizing epithelium lining the surface and the crypts of human palatine tonsils was analyzed by high-resolution gel electrophoresis, immunoblotting, and immunohistochemical techniques. In contrast to the superficial epithelium, which showed a fairly constant keratin composition consisting of the neutral-to-basic keratins K4, K5, K6, and K8 and the acidic keratins K13, K14, K16, and K19, the keratin profiles of tonsillar crypt epithelial cells were found to be more variable, particularly with respect to the expression levels of K4 and K13. These were identical to those of surface epithelium, reduced, or abolished. Since K4 and K13 characterize the mature stage of differentiation in squamous nonkeratinizing epithelia, their decrease is indicative of an incomplete epithelial differentiation. Immunohistochemical analyses confirmed this hypothesis and allowed us, furthermore, to correlate the expression of K13 with the morphologic alterations of tonsillar crypt epithelium in the course of reticulation.

KEY WORDS — biochemical and immunohistochemical analysis, epithelial differentiation, keratin expression, palatine tonsil, tonsillar crypt epithelium.

INTRODUCTION

Human palatine tonsils are lined, on their surface, by a nonkeratinizing stratified squamous epithelium that extends continuously into the branching system of tonsillar crypts. The particular function of the palatine tonsil with respect to the immunoprotection of an individual, however, brings about profound morphologic changes in the tonsillar crypt epithelium, termed reticulation. The regular stratified arrangement of epithelial cells is loosened and immunoreactive cells such as lymphocytes, plasmocytes, and macrophages invade the epithelium to directly contact the outside and handle antigens. While these fine structural changes in the course of reticulation have been studied,[1-5] the underlying concomitant molecular events and alterations still remain to be investigated.

Recent studies have indicated that the keratin proteins can serve as excellent markers for different types and pathways of epithelial differentiation and have also established their usefulness in tumor typing.[6-8] As specific constituents of the 10-nm (intermediate-size) filaments in almost all epithelial cells, keratins (or cytokeratins) belong to a heterogeneous family of acidic ($pI<5.5$) and neutral-to-basic ($pI >5.5$) proteins ranging in apparent molecular weight from 40,000 to 70,000 d. Of the more than 20 human keratins described and catalogued so far,[9,10] different members are detected in the diverse epithelial tissues, and each epithelial cell expresses only a few, frequently as coordinated pairs consisting of one neutral-to-basic and one acidic keratin.[11,12]

In this paper we report on the patterns of keratin expression in epithelial cells lining the crypts of human palatine tonsils. In comparison to the superficial cell layers of tonsils, the cryptal epithelium showed qualitative and quantitative alterations that concerned particularly keratins K4 (a ν b, where ν = and/or) and K13. The differential expression of these keratins could be correlated in immunohistochemical analyses to the morphologic alterations that tonsillar crypt epithelium undergoes in the course of reticulation and thus should reflect the different capabilities of tonsillar crypt epithelial cells to reach an advanced stage of differentiation.

MATERIALS AND METHODS

Tissues. Palatine tonsils were obtained from 79 patients, 40 of whom were female and 39 of whom were male, who underwent elective tonsillectomy. Ages ranged from 3 to 45 years (mean, 15.3 years).

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Presented in part at the 58th Annual Meeting of the German Society of Otorhinolaryngology–Head and Neck Surgery, Bad Neuenahr, Germany, May 31–June 4, 1987.

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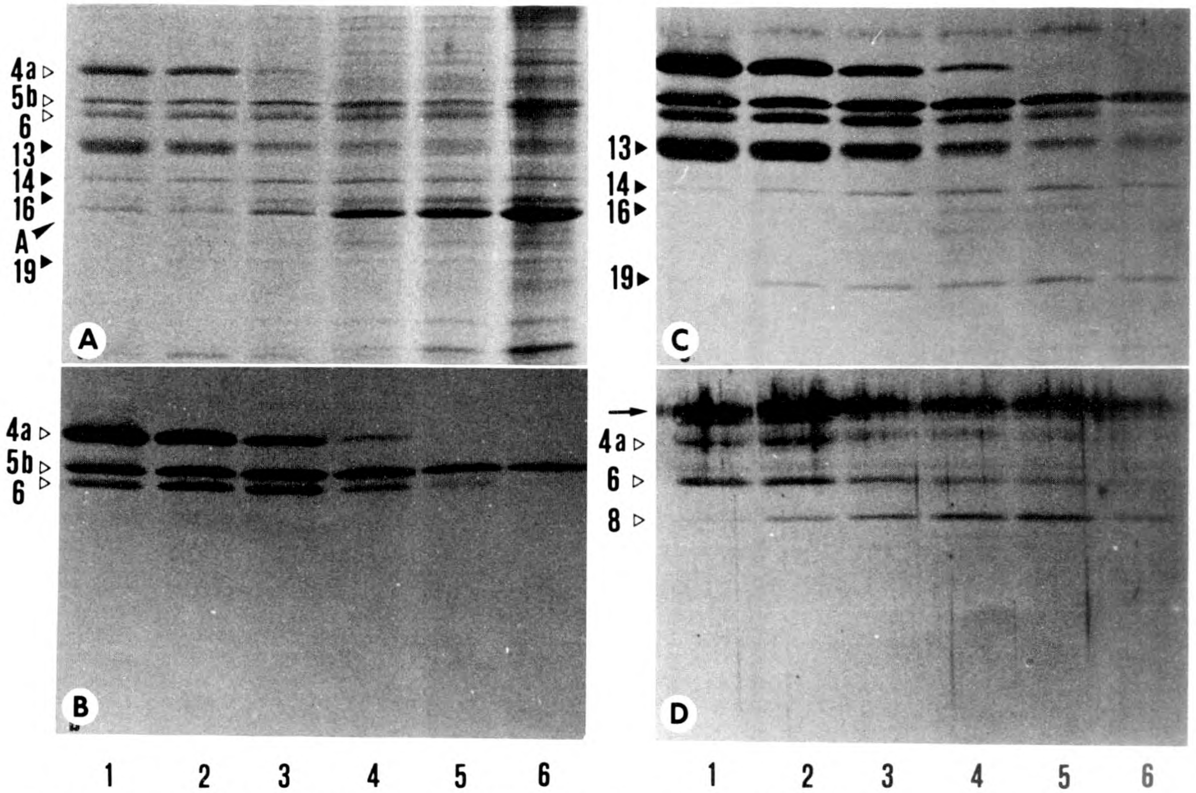


Fig 1. Sodium dodecyl sulfate polyacrylamide gel electrophoresis and immunoblot analysis of cytoskeletal proteins present in superficial and cryptal epithelium of human palatine tonsils. Cytoskeletal residues represent surface epithelium (lane 1) and five different preparations of cryptal epithelium (lanes 2 through 6). Keratins are numbered according to catalogue of human cytokeratins[9] with consideration of polymorphic keratins.[14,15] A) Coomassie blue–stained gel. A — actin. B-D) Corresponding immuno recognition patterns on nitrocellulose paper. B) Polyclonal rabbit antikeratin antiserum 10-2/2 exclusively reactive to neutral-to-basic keratins. C) Reprobing of B using polyclonal antiserum 8-2/4 to display acidic keratins. D) Monoclonal antikeratin antibody KL-1. Arrow — ubiquitous keratinous contaminant[20] detected by monoclonal KL-1 antibody in addition to its ability to react with keratins K4, K5, K6, and K8 as well as keratin K10 (not shown; see Viac et al[17]).

For routine histopathologic and immunohistochemical examinations, tissues were fixed in formalin and embedded in paraffin, while tissue samples for biochemical analyses were processed immediately or after storage at −70°C.

Cytoskeletal Preparations. Tonsillar crypts were irrigated several times with ice-cold Ca^{2+}- and Mg^{2+}-containing Hepes-buffered Earle's balanced salt solution with use of a blunt-ended needle in order to remove the cryptal contents (mainly detritus). Specimens were then heated in the solution at 60°C for 5 minutes to allow for easy dissection of the epithelium.[13,14] After removal of all of the superficial epithelium, the irrigated crypts were incised and the cryptal epithelium was obtained under microscopic control with a small sharp spoon from an area as deep as possible to avoid contamination with surface epithelium. Epithelial tissue samples were homogenized and extracted in the presence of protease inhibitors as described.[14] The resulting Triton–high salt resistant pellet, highly enriched in keratins, was solubilized in sample buffer for gel electrophoresis.

Gel Electrophoresis and Immunoblot Analysis. One-dimensional sodium dodecyl sulfate polyacrylamide gel electrophoresis, two-dimensional separations employing the nonequilibrium pH gradient technique, and immunoblotting of separated polypeptides were performed as described.[14,15] Nitrocellulose filters were incubated with a set of polyclonal antikeratin antisera raised in rabbits against chromatographically purified keratins,[15,16] the monoclonal antikeratin antibody KL-1,[17] or the monoclonal antivimentin antibody V9.[18] Secondary antibodies were horseradish peroxidase–conjugated goat anti rabbit immunoglobulins being developed with 4-chloro-1-naphthol and hydrogen peroxide as described.[15] The mouse monoclonal primary antibodies were bridged via rabbit anti mouse immunoglobulins to the peroxidase-coupled antibodies.

Immunohistochemistry. Immunohistochemical analyses were performed according to the alkaline phosphatase–antialkaline phosphatase technique of Cordell et al.[19] The mouse monoclonal antibodies KS13.1 (Dianova, Hamburg, Germany) and V9 (Dakopatts, Hamburg) were used to detect keratin K13 and vimentin, respectively.

RESULTS

Keratin Expression Patterns in Tonsillar Epitheli-

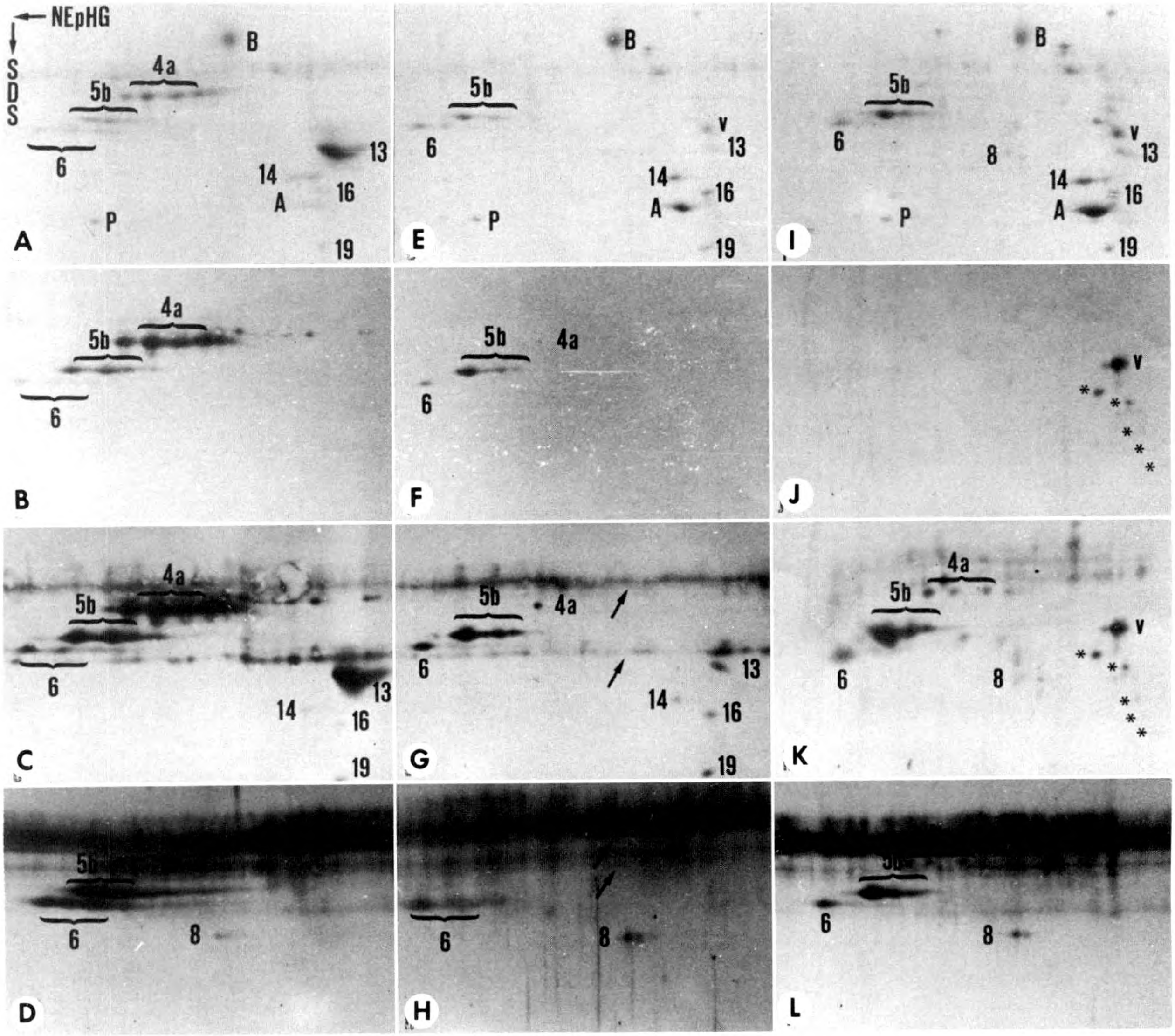
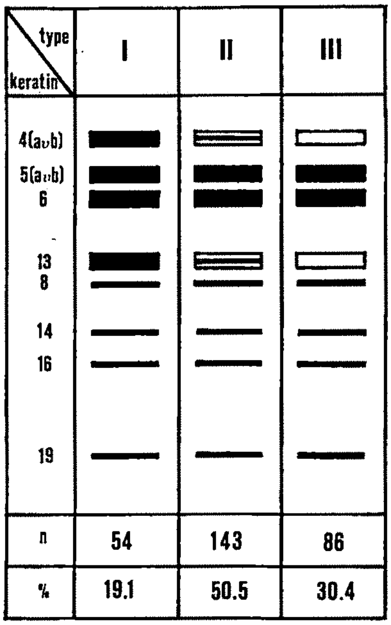


Fig 2. Two-dimensional separation of cytoskeletal proteins obtained from A-D) surface epithelium and E-H,I-L) two different crypts of human palatine tonsils. A,E,I) Coomassie blue-stained gels. B,F) Corresponding immunoblots with polyclonal antiserum 10-2/2 to detect basic keratins. C,G) Reprobing of B and F with polyclonal antiserum 8-2/4 against acidic keratins to establish complete keratin pattern. D,H,L) KL-1 monoclonal antibody. J) Antivimentin monoclonal antibody V9. K) Reprobing of J with antiserum 10-2/2. NEpHG — direction of first dimension using nonequilibrium pH gradient electrophoresis (basic polypeptides are to left), SDS — direction of second dimension in presence of sodium dodecyl sulfate. Keratins are numbered as described in Fig 1. Brackets enclose isoelectric variants of same protein. Coelectrophoresed marker polypeptides are bovine serum albumin (B; apparent molecular weight 68 kd; pI 6.35) and yeast phosphoglycerate kinase (P; apparent molecular weight 43 kd; pI 7.4). A — residual actin, v — vimentin, asterisks — "staircase" of spots typical of proteolytically affected vimentin molecules,[22] arrows — ubiquitous keratin contaminants detected by some antikeratin antibodies.

um. One-dimensional gel electrophoretic separations of cytoskeletal proteins prepared from the superficial epithelium of palatine tonsils (lane 1) and five different tonsillar crypts (lanes 2-6) are shown in Fig 1.[9,14,15,17,20] Typically, the surface epithelium displayed only a few abundant proteins on Coomassie blue–stained gels, while the profiles of cryptal samples appeared to be more heterogeneous, occasionally lacking some of the proteins prominent in superficial epithelium and containing additional, although mainly minor, polypeptides (Fig 1A). Identification of keratins was accomplished in the corresponding immunoblots: keratins of the neutral-to-basic subfamily, namely the members K4a, K5b, and K6, were elicited by the polyclonal antikeratin antiserum 10-2/2 (Fig 1B) and the members of the acidic subfamily, ie, K13, K14, K16, and K19, were detected on the same blot following reaction with antiserum 8-2/4 (Fig 1C). In one, this immunoblot presented also the entire spectrum of keratins expressed in these specimens except for keratin K8, which was detected by the monoclonal antikeratin antibody KL-1 (Fig 1D).

The keratin pattern shown for the surface epithelium of palatine tonsils (lane 1) is typical of the stratified squamous, primarily nonkeratinizing epithelium lining the major part of the upper digestive



keratin \ type	I	II	III
4(a∨b)	▬	═	▭
5(a∨b)	▬	▬	▬
6	▬	▬	▬
13	▬	═	▭
8	—	—	—
14	—	—	—
16	—	—	—
19	—	—	—
n	54	143	86
%	19.1	50.5	30.4

Fig 3. Classification of keratin patterns in tonsillar crypt epithelium and their frequency. Schematic presentation according to one-dimensional separations. ∨ — and/or, filled bar — amount as in surface epithelium of palatine tonsils, split bar — variably reduced amounts, empty bar — low to undetectable levels.

tract.[6,7,9,14,21] In contrast, the keratin patterns of tonsillar crypts were found to be much more variable, both in composition and in quantity of particular members expressed. Thus, we have found keratin patterns of crypt epithelium that were almost identical to those of the surface epithelium (lane 2), while in others the amount of K4 and K13 was reduced to a different (lanes 3 and 4) or even an undetectable (lanes 5 and 6) level. In addition, K6 was reduced in some samples, while K8 and K19, being hardly detected in superficial epithelium, were present in increased amounts but did not vary considerably among the different cryptal samples.

Two-dimensional separations of cytoskeletal proteins of surface epithelium (Fig 2A-D[22]) and of two different samples of crypt epithelium (Fig 2E-H and Fig 2I-L, respectively) allowed us to distinguish the keratins according to charge and size and provided the basis for the nomenclature used.[9,14] Again, the major difference concerning the expression of keratins resided in the considerable reduction of K4 and K13 seen in crypt epithelium. Vimentin, the intermediate filament protein specific to mesenchymal cells, gave evidence of the contribution of lymphatic tissue to the samples taken from tonsillar crypts and was identified by the monoclonal antibody V9 (Fig 2E,I,J,K). Its presence in cryptal samples does not, however, interfere with our conclusions outlined below.

Classification of Keratin Patterns Expressed in Tonsillar Crypt Epithelium. On the basis of the analyses of 238 tissue samples of tonsillar crypt epithelium obtained from 79 patients, three types of keratin patterns could be discerned (Fig 3). Type I patterns (eg, Fig 1, lane 2) were almost identical to the pattern of superficial epithelium and were found in about 20% of the specimens. Type II patterns occurred most frequently (50%) and displayed a variable reduction of K4 and K13 as exemplified in lanes 3 and 4 of Fig 1. Type III patterns were observed with a frequency of about 30% and were characterized by very low to almost undetectable levels of these keratins (compare Fig 1, lanes 5 and 6). This variation apparently did not depend on the clinical state of the tonsils or the age of the patient; rather, we have found patterns belonging to different types within one tonsil and even along one particular crypt (see also below and Fig 4).

Expression of Keratin K13 in Tonsillar Crypt Epithelium. Immunohistochemical analyses were performed to investigate how the alterations observed in the keratin patterns correlated to the morphologic facets of this epithelium. Figure 4 shows formalin-fixed and paraffin-embedded tissue sections of tonsillar crypts and the surface epithelium stained either with a monoclonal antibody that allowed us to monitor the specific distribution of K13 or with an antivimentin antibody.

In surface epithelium the K13 antibody characteristically stained the suprabasal cell layers but not the basal cells (Fig 4B). This is quite similar to the staining pattern found in tonsillar crypts showing a regularly stratified epithelium (Fig 4F). In areas showing reticulation the epithelial organization is loosened and the epithelial cells are typically arranged in a netlike formation (Fig 4G). Among these, several cells still expressed keratin K13, but many others, usually located more basally, were negative (compare Fig 4C and 4D). In reticulated epithelium the number of keratin K13–positive cells as well as the staining intensity generally decreased and thus led us to conclude that the reduction of keratin K13, and consequently its basic partner K4, is correlated with the stage of reticulation in tonsillar crypt epithelium.

DISCUSSION

In the context of the now widely accepted notion that regards keratins as sensitive molecular indicators for the different routes and stages of epithelial differentiation,[6-8] the present paper is concerned with the analysis of keratins in epithelial cells of human palatine tonsils, in particular those lining the tonsillar crypts. The crypt epithelium is, like the surface epithelium, a squamous nonkeratinizing tissue. The surface epithelium of palatine tonsils can be easily dissected in sheets from the underlying connective tissue upon heating.[14] In contrast, the close association of epithelial and lymphatic tissue, characteristic of the lymphoepithelial organs belonging to the ring of Waldeyer and particularly re-

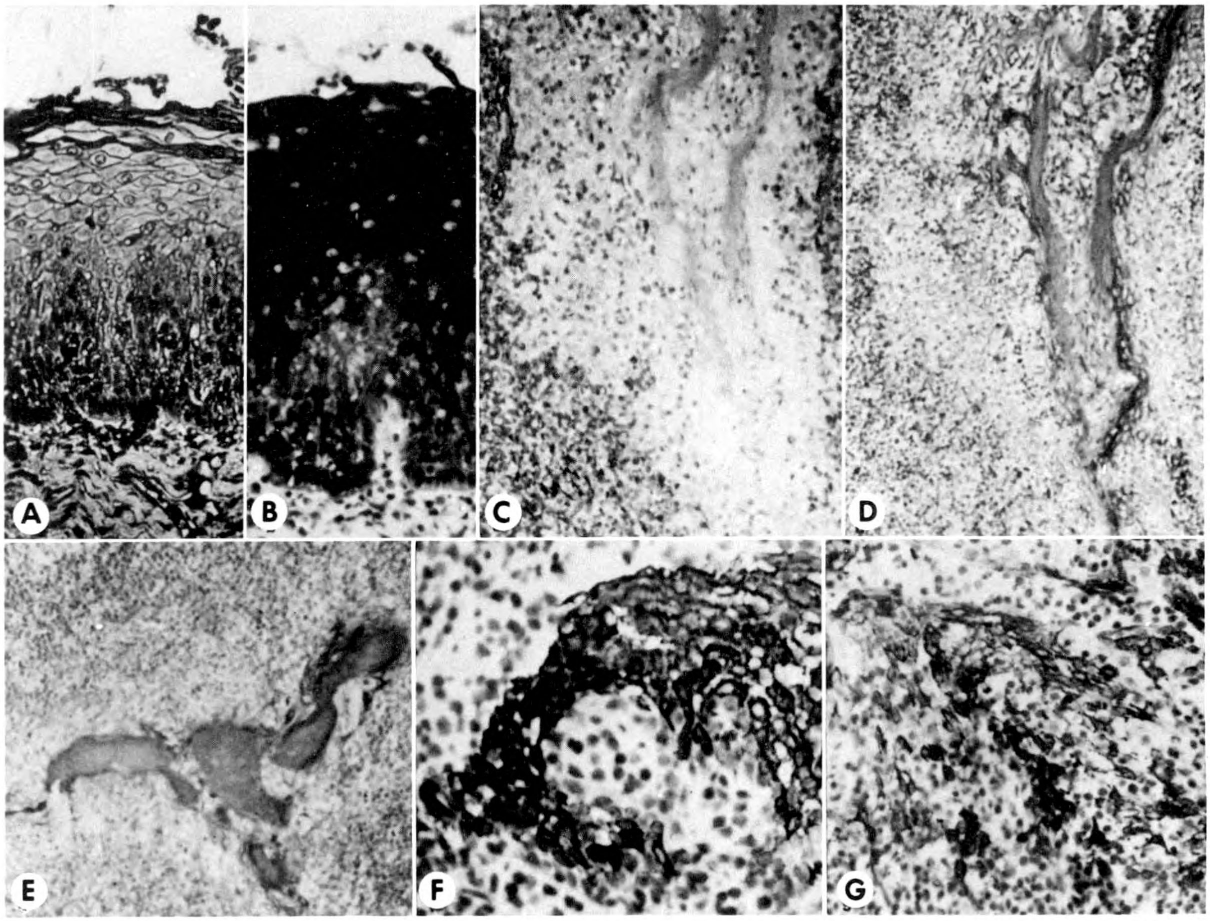


Fig 4. Immunohistochemical detection of keratin K13 in human tonsillar crypt epithelium. Formalin-fixed, paraffin-embedded sections reacted with K13 monoclonal antibody Ks13.1 (B,D-G) or vimentin antibody V9 (A,C) and detected by alkaline phosphatase–antialkaline phosphatase technique. A,B) Surface epithelium of palatine tonsil (original x500) and C,D) tonsillar crypt descending from surface as found in same specimen (original x330). E) Bottom of crypt showing high degree of reticulation and very few K13-positive cells as well as luminal detritus (original x350). F,G) Cryptal areas from one specimen with F) almost regularly stratified epithelium (original x800) and G) typical netlike formation of epithelial cells (original x500).

flected in the reticulation of the epithelium,[1,2,5] did not permit us to retrieve pure epithelial tissue samples from the tonsillar crypts. However, the use of antibodies of known specificity in combination with high-resolution gel electrophoresis and immunoblotting allowed us to identify unequivocally the constituent water-insoluble (ie, intermediate) filament proteins of their cytoskeleton and revealed changes in the keratin pattern that reflected the various degrees of reticulation of tonsillar crypt epithelium.

Since all of the patterns analyzed contained keratin K5 (a ν b) (in accordance with the notion that the keratin pair K5/K14 may serve as a molecular marker for keratinocytes, the major cell type of stratified epithelia[6,7,9,11]), these proteins were used as a reference to adjust the sample loadings for equal staining on gels and immunoblots. In comparison to the superficial cell layers of tonsils, the cryptal epithelium showed qualitative and quantitative alterations that concerned particularly keratins K4 and K13. These two keratins were 1) present in the same amounts as in surface epithelium, 2) reduced, or 3) undetectable. As the keratin pair K4/K13 is considered to characterize biochemically the most advanced stage of differentiation in squamous nonkeratinizing epithelia lining the upper digestive tract,[7,9,14] reduced levels may be indicative of an incomplete and/or disrupted epithelial differentiation in about 80% of the tonsillar crypts sampled. An increased contribution of immature keratinocytes (ie, basal and parabasal cells) in the samples is also manifested by the moderate increase of keratins K8 and K19. Differentiation of tonsillar crypt epithelium may then be classified as ranging from the "surface type" to the "basal cell type."

Moreover, since the differential expression of these keratins and, in particular, of keratin K13 could be correlated to the morphologic alterations that tonsillar crypt epithelium undergoes in the course of reticulation,[1,2,4,5] the different capabilities of tonsillar crypt epithelial cells to reach an advanced stage of differentiation can be determined by use of keratins as molecular markers.

That the observed spectrum of keratin expression patterns in tonsillar crypt epithelium resembles that of the epithelial lining of lateral cervical cysts[16] confirms our previous conclusion that lateral cervical cyst epithelia faithfully perform the differentiation programs typical of upper digestive tract squamous epithelia. With respect to the question of the origin of lateral cervical cysts, ie, whether they are congenital or acquired (see Wild et al[16] and references therein), our results then lend further support to our hypothesis that the inner lining of lateral cervical cysts is derived from Waldeyer's ring epithelial cells that settle and "transform" a neck lymph node to form an epithelium that is competent to imitate the crypts of the palatine tonsil and to cover part of their function, for example in antigen handling.

ACKNOWLEDGMENTS — We thank Professor Jobst von Scheel for his continuing interest and encouragement. Dr Genka particularly acknowledges the support provided by Professor Yutaka Noda (Head of the Department of Otolaryngology, University of Ryukyus, Okinawa, Japan). Part of this work was done by Dr Genka in partial fulfillment of the requirements for the MD degree of the Free University of Berlin.

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HUMAN IN VITRO NASAL AND TRACHEAL CILIARY BEAT FREQUENCIES: COMPARISON OF SAMPLING SITES, COMBINED EFFECT OF MEDICATION, AND DEMOGRAPHIC RELATIONSHIPS

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In vitro nasal and tracheal ciliary beat frequencies (CBFs) were measured photometrically in brush samples of 15 patients undergoing bronchoscopy. Tracheal and nasal CBF values in these patients were found to be significantly correlated ($r = .74$, $p < .01$), and the latter did not differ significantly from the nasal CBF of 80 subjects serving as controls. Premedication with morphine and atropine and local anesthesia with lidocaine hydrochloride significantly decreased the CBF. Among the control subjects, a significantly higher CBF (13.6 ± 1.5 Hz) was found in the young age group (10 to 19 years) as compared to other groups (12.2 ± 1.7 Hz). Gender and ethnic origin did not influence CBF in any age group. These data support the possible use of the in vitro study of nasal epithelium to reflect the CBF in the lower respiratory tract.

KEY WORDS — bronchiectasis, cilia, ciliocytophthoria, Kartagener's syndrome, respiratory tract.

INTRODUCTION

In recent years a great deal of interest has been generated about the structure and function of cilia throughout the body and in particular the cilia of the respiratory tract. This interest is in part due to the recent description of the syndrome of "immotile" or "dyskinetic" cilia.[1]

Mucociliary clearance, an essential element in the defense system of the tracheobronchial tree, depends in great part on effective beating of cilia. Assay of mucociliary clearance has been approached by actually measuring the in vivo clearance rates of inhaled radiopaque or radiolabeled particles from the large airways.[2] This approach assesses the combined interaction of ciliary movement and respiratory secretions, precluding the analysis of their separate contributions; hence the search for a simple in vitro technique concentrating on estimation of the ciliary factor.[3]

The in vitro estimation of ciliary function has depended upon the measurement of the beat frequency of cilia observed in cell samples taken from the tracheobronchial tree.[4] The major airways are indeed the ideal source for the ciliated cells, but obtaining these cells requires an invasive procedure and use of premedication and local anesthesia. Nasal cells are far more accessible, and most recent studies of the ciliary beat frequency (CBF) in patients have used nasal biopsy, curettage, or brush specimens.[4-13] In these reports it has been assumed that as the nose is part of the respiratory system, the CBF of nasal cells reflects the CBF of cells in the lower respiratory tract. It has been further assumed that premedication or local anesthesia given to subjects prior to sampling had no effect on the results, and in all reports there is no special attention given to the age of the patients, their sex, or ethnic origin.

In the current study the in vitro CBFs in nasal and tracheal ciliated cells taken from the same subject were compared, the effect of premedication and local anesthesia was checked, and analysis of the relationships between ciliary activity and age, sex, and ethnic origin was carried out. The results were compared with those of previous studies addressing similar questions.

METHODS

Ninety-six subjects were included in this study. Ciliated cells were obtained from one nasal cavity and the trachea of 16 patients undergoing fiberoptic bronchoscopy (FOB). Nasal specimens were obtained from 80 normal nonsmoking nonatopic subjects. To assess the effect of premedication and local anesthesia on the CBF, nasal specimens were obtained from the patients before and after premedication and local anesthesia, so that each patient served as his or her own control. No premedication or local anesthesia was given to the normal controls. All procedures were approved by the Helsinki Committee of the Chaim Sheba Medical Center.

Nasal mucosal cells were obtained from the superior aspect of the inferior turbinate with a standard cytology brush (Meditech, Cooper Science Corp). The nasal specimens were obtained prior to FOB. The FOB was performed via the nose with an Olympus (Lake Success, NY) BF-2 fiberoptic bron-

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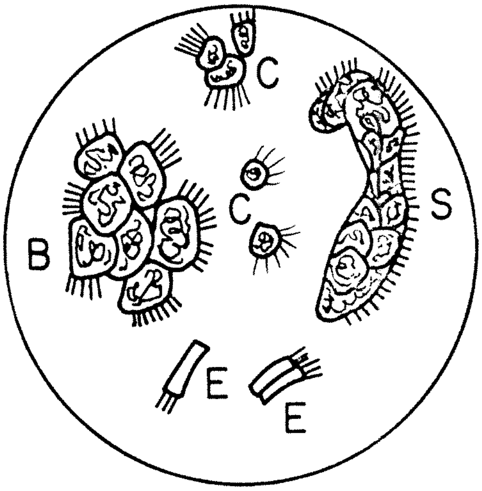

Fig 1. Illustration of typical sample. S — strip of ciliated epithelium, B — bunch of ciliated cells, C — cuboidal ciliated cells, E — elongated ciliated cells.

choscope. Subjects undergoing bronchoscopy were premedicated with morphine sulfate (5 to 10 mg) and atropine sulfate (1 mg) intramuscularly. For local anesthesia, 2 to 3 mL of a 2% lidocaine hydrochloride solution was sprayed in the nose and 1 mL of a 4% solution was applied to the vocal cords. The trachea was anesthetized with 2 mL of lidocaine hydrochloride 2% delivered through the bronchoscope. Tracheal brushings were taken from the anterior tracheal wall, approximately 3 cm above the major carina, by use of a sheathed cytology brush (Meditech).

Immediately after each specimen was obtained, cellular material adhering to the brush was dislodged by agitation in a small vial containing 1.5 mL of nutrient medium. Our medium consisted of modified Eagle's medium (GIBCO, Grand Island, NY) with 0.1 g/L sodium hydrogen carbonate, 2.1 g/L sodium chloride, and 10 mmol/L Hepes (*N*-2-hydroxyethyl-piperazone-N′-2-ethanesulfonic acid) buffer (pH 7.3). Like most of the tissue culture media, modified Eagle's medium is bicarbonate-buffered and thus is suitable for use in closed systems with a carbon dioxide–enriched atmosphere. In open air, carbon dioxide volatilizes and the medium becomes alkaline. In order to maintain the desired pH, most of the bicarbonate was replaced with the widely used Hepes buffer, and the ionic strength of the solution was maintained by the addition of sodium chloride.

For an initial assessment, 1 or 2 drops of the sample were examined in a standard hemocytometer (Hauser Scientific, New York, NY) with a light microscope (Olympus KHS) at 10 x 40 magnification. The microscope's stage was warmed to approximately 35°C by a simple table lamp. Figure 1 illustrates the types of cellular clusters encountered as viewed through the microscope. Strips of ciliated epithelium and bunches of ciliated cells were the forms most commonly seen. Also observed were single or small groups of 2 or 3 cuboidal or elongated ciliated cells. The heavily ciliated edges of the strips and the bunches were the preferred sites for the CBF measurements. On the whole, about 1,500 ciliated cells are obtained per sample with this method. The cuboidal and the elongated cells differ in their ciliature. The cuboidal cells, which make up the majority, have short, rapid and metachronously beating cilia, while the elongated ones have longer and fewer cilia that are usually immotile but sometimes move very slowly. The elongated cells are probably older shedded cells of the nasal epithelium. They were excluded from the CBF measurements.

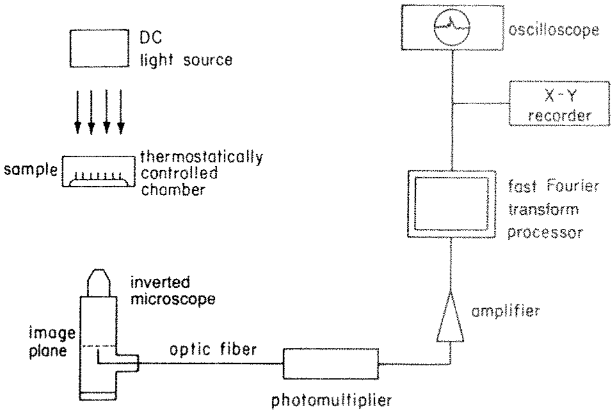

Fig 2. Schematic diagram of measuring system.

The CBF was measured from the profiles of strips and bunches of ciliated epithelium and from single nonvibrating ciliated cells with use of a phase-contrast microscope at 10 x 40 magnification. Measurements were repeated at least 5 times, each time by measuring different randomly selected strips or cells of the specimen. Samples were examined inside a small glass chamber at 35°C. This temperature was maintained by circulating thermostatically controlled water through a double-walled jacket around the chamber. The chamber was covered in order to minimize possible evaporation, but it was not sealed. All measurements were done within 4 hours of specimen collection. Part of this time was required for the transfer of the vials containing the samples, at ambient temperature, from the hospital to the laboratory. In preliminary experiments it has been verified that no significant change in CBF occurs for 9 hours after specimen collection.

The measuring system developed for objective and automatic estimation of beat frequencies of small bundles of cilia is shown schematically in Fig 2. It consists of an inverted phase-contrast microscope (Nikon MS, Japan), whose ocular (model 700-10-36A, Gamma Scientific EGC, San Diego, Calif) is provided with a fine optic fiber (50 μm in diameter) precisely positioned at the image plane. The light passing through the moving cilia is collected by the optic fiber and transmitted to a sensitive photomultiplier (9558B, EMI, London, Eng-

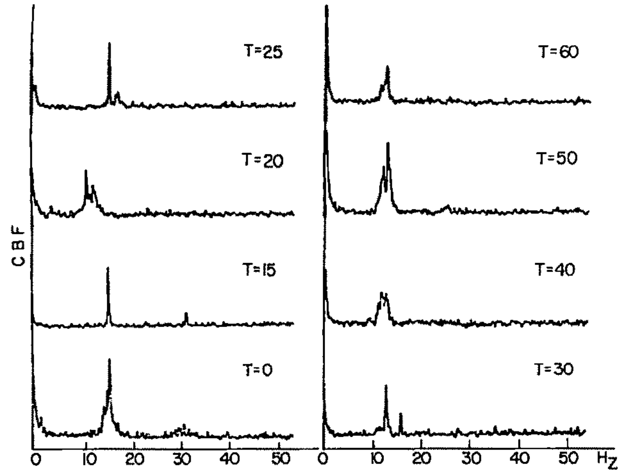

Fig 3. Representative set of ciliary beat frequency (CBF) distribution curves taken from different sites of same specimen within 1 hour. T — time in minutes.

land). The electric signal produced corresponds to the light intensity observed by the tip of the optic fiber. This signal is fed into a differential amplifier and an analog-to-digital convertor. It is then analyzed on-line by a fast Fourier transform processor (model 4520, Unigon, Mount Vernon, NY) to produce the distribution of frequencies and their corresponding incidence at the original signal. This distribution is continuously accumulated and displayed on the screen of an oscilloscope. It can be copied at will with the aid of an x-y plotter. When ciliated tissue is being measured by the system, fluctuations of light intensity caused by movement of the 5 to 10 observed cilia are accumulated (during the measuring period of about 20 seconds) and automatically transferred into the frequency domain. Usually, the entire distribution builds up as a narrow peak containing the dominant frequency governing the beat. A representative set of actual distribution curves taken from different sites of the same specimen within 1 hour is exhibited in Fig 3.

Among the control subjects, the mean CBF in four age groups was compared by one-way analysis of variance with internal comparisons by *t* test using error mean square. The differences between the genders as well as between the two ethnic origin groups (European and Oriental, as defined by Goodman[14]) were compared separately within age groups under and over 20 years by *t* test for independent samples. This test was also used in comparison of the nasal CBF before medication in the 16 FOB patients to that of the normal controls.

TABLE 1. MEAN CILIARY BEAT FREQUENCIES (±SD) OF NASAL SAMPLES TAKEN FROM NORMAL SUBJECTS, BY AGE

Age Group (yr)	*No.*	*Ciliary Beat Frequency (Hz)*
10-19	35	13.6±1.5
20-29	13	12.6±2.6
30-39	22	12.1±1.4
40-80	10	12.0±1.2

TABLE 2. MEAN CILIARY BEAT FREQUENCIES (±SD) OF NASAL SAMPLES TAKEN FROM NORMAL SUBJECTS, BY GENDER AND AGE

Age Group (yr)	*Gender*	*No.*	*Ciliary Beat Frequency (Hz)*
10-19	Male	22	13.5±1.3
	Female	13	13.9±1.8
20+	Male	28	11.8±1.4
	Female	17	12.9±2.0

Comparison of the nasal CBF before and after medication, as well as nasal and tracheal CBFs after medication, was done by *t* test for paired samples, based in each comparison on subjects for whom paired observations were available. The association between the postmedication nasal and tracheal CBFs was also evaluated by Pearson's correlation coefficient, testing the significance of its difference from zero. Means are presented throughout the text, followed by standard deviations.

RESULTS

The mean (±SD) nasal CBF values for the 80 normal control subjects are displayed in Tables 1-3.

There was no significant difference in the CBF between age groups above the age of 20 years. The mean CBF for all those subjects was 12.2±1.7 Hz. The mean CBF in the 10- to 19-year-old age group was significantly ($p<.001$) higher than in all other age groups: 13.6±1.5 Hz.

No significant differences were found in age groups under or over 20 years between males and females or between subjects of European or Oriental origin.

Table 4 lists the clinical details of the FOB patients. There were eight males and eight females with a mean age of 53.7±18.7 years (range, 16 to 80), of whom seven had a history of smoking. The "clinical details" column of the Table indicates briefly the reason for the bronchoscopy and its findings. In all cases but one (case 6), no pathologic findings were observed in the trachea. Nine of the patients did not have other systemic diseases and were not taking any medications. Patient 1 had a history of heavy drinking. Patient 7 had uterine adenocarcinoma with metastases in the lungs and was receiving pentazocine hydrochloride analgesia. Patient 9 had diabetes mellitus and was receiving chlorpropamide. Patient 15 was receiving propranolol hydrochloride for idiopathic hypertrophic sub-

TABLE 3. MEAN CILIARY BEAT FREQUENCIES (±SD) OF NASAL SAMPLES TAKEN FROM NORMAL SUBJECTS, BY ETHNIC ORIGIN AND AGE

Age Group (yr)	*Ethnic Origin*	*No.*	*Ciliary Beat Frequency (Hz)*
10-19	European	22	13.6±1.4
	Oriental	13	13.6±1.6
20+	European	10	12.6±2.2
	Oriental	35	12.1±1.6

TABLE 4. SUMMARY OF CLINICAL DETAILS OF BRONCHOSCOPY PATIENTS

No.	*Age (yr)*	*Sex*	*Ethnic Origin*	*Smoking History*	*Clinical Details*
1	68	M	O	+	Lung cancer
2	48	M	E	+	Lung cancer
3	36	F	O	+	Bronchiectasis
4	64	F	E	–	Bronchiectasis
5	56	M	E	+	Lung cancer
6	47	M	O	+	Tracheobronchitis
7	70	F	O	–	Metastatic lung cancer
8	31	M	E	–	Acute bronchitis
9	56	F	E	–	Sarcoidosis
10	68	M	E	+	Lung cancer
11	80	M	E	+	Lung cancer
12	18	F	O	–	Kartagener's syndrome
13	26	F	E	–	Cough; no pathologic findings
14	70	F	E	–	Lung cancer
15	68	M	E	–	Lung cancer
16	16	F	O	–	Kartagener's syndrome

O — Oriental, E — European.

aortic stenosis. Patients 12 and 16 were sisters with Kartagener's syndrome who underwent FOB as part of their clinical assessment. Patient 16 was in better general condition then her sister and her lung disease was less severe.

Table 5 presents the mean nasal CBF values of samples obtained before the premedication and the local anesthesia and afterward, as well as the CBF values of the tracheal samples, which were all obtained after premedication and local anesthesia. The mean nonmedication nasal CBF did not differ significantly from the mean nasal CBF in the control population. The postmedication nasal CBF was significantly lower compared to the nonmedication level, but the difference was small (mean difference, 1.29±1.39 Hz; $p<.001$).

No significant difference was observed between the mean postmedication nasal and tracheal CBFs (mean difference, 0.45±2.42 Hz; $p>.30$). A significant positive correlation was found between the postmedication nasal and tracheal CBFs ($r=.74$; $p<.01$; 95% confidence limits, 0.32 and 0.92).

DISCUSSION

The nasal and tracheal CBF values reported in the present work are well within the range of those reported for humans by others.[6,8,15,16]

The significant strong and positive correlation between nasal and tracheal CBFs and the similarity of their mean CBFs confirm the results of previous studies.[6,13,16,17] The majority of those studies[13,16,17] compared nasal to bronchial and not tracheal samples. As the trachea is a central part of the pulmonary mucociliary defense system, a tracheal evaluation is essential, as was done in the present study and in the report of Rutland et al.[6] Good correlation between the tracheal CBF and that of segmental bronchi and smaller airways has also been reported.[6,18] Despite some methodological differences such as in medications used or methods of measurement, the final outcome of all the studies is similar: namely, uniformity of ciliary motion along the respiratory tract. This uniformity supports the notion that nasal epithelium can be used to reflect the ciliary activity, at least as measured in vitro, in the trachea and probably in much of the rest of the respiratory tract.

TABLE 5. MEAN CILIARY BEAT FREQUENCIES (±SD) OF NASAL AND TRACHEAL SAMPLES TAKEN FROM BRONCHOSCOPY PATIENTS

	Ciliary Beat Frequencies (Hz)		
No.	*Nasal I*	*Nasal II*	*Tracheal*
1	Not measured	9.2±2.1 (5)	7.2±2.7 (5)
2	Not measured	9.3±1.2 (6)	10.8±2.0 (12)
3	Not measured	12.5±2.9 (6)	10.0±1.3 (6)
4	Not measured	12.7±1.6 (15)	14.5±1.4 (10)
5	Not measured	11.8±1.1 (6)	12.8±2.1 (6)
6	15.3±2.2 (9)	13.7±4.5 (15)	14.7±4.1 (11)
7	10.6±3.9 (15)	8.7±0.8 (8)	9.4±2.4 (11)
8	10.1±1.2 (5)	9.9±1.7 (6)	10.0±2.0 (7)
9	11.9±1.0 (12)	11.3±1.4 (18)	11.9±2.9 (9)
10	11.9±2.3 (7)	8.4±1.4 (5)	9.4±1.3 (5)
11	13.4±3.8 (8)	13.3±2.5 (9)	11.3±2.3 (10)
12	12.9±1.9 (10)	10.3±1.5 (10)	11.4±2.5 (6)
13	13.5±1.6 (9)	14.4±1.6 (12)	Not measured
14	10.7±1.9 (11)	8.7±0.8 (7)	Not measured
15	11.9±2.4 (6)	Not measured	9.5±1.6 (12)
16	11.9±3.2 (10)	6.0 (1)	5.8±2.2 (10)
Mean	12.2±1.6 (n=10)	11.0±2.1 (n=14)	11.0±2.1 (n=13)
Mean difference	1.29±1.39 (n=9)*	0.45±2.42 (n=13)†	

Each value represents mean of repeated measurements, number of which is presented in parentheses.

Nasal I — before premedication and local anesthesia, nasal II — after premedication and local anesthesia.

*Nasal I versus nasal II (n = number of pairs).

†Nasal II versus tracheal (n = number of pairs).

Ciliary function is suspected to be involved in the pathogenesis of Kartagener's syndrome,[1] bronchiectasis,[19] and secretory otitis media.[20] The study of the easily obtained nasal samples for the evaluation of tracheobronchial ciliary activity among patients has been reported by several laboratories.[4,6-8,15,16,21] A few basic assumptions must be considered, however.

First, it is assumed that the in vitro examination of CBF reflects the beat frequency in vivo. Although a large difference is not expected, this assumption should be checked. So far, only Reimer et al[22] have tried, albeit inconclusively, to compare the in vivo and in vitro mucociliary activities in human maxillary sinuses.

Second, it is assumed that a defect in the nasal in vitro ciliary motility, when found, reflects a similar aberration in the lungs, and conversely — that a defect in the cilia in the lungs is accompanied by impaired nasal ciliary activity. This assumption lacks direct proof, as only patients without defective ciliary motion were examined previously[6,13,16] and in the present study. Two Kartagener's syndrome patients and two bronchiectasis patients were included in our group, but no abnormalities in the in vitro CBF were demonstrated. Unfortunately, no electron microscopy was performed on these patients. Other Kartagener's syndrome patients, with immotile nasal cilia or low nasal CBFs, were not available for FOB examination.

Another problem that still requires further study is whether the nasal and the tracheobronchial beat frequencies reflect the ciliary activity in the most distal small airways, where some of the pathologic processes actually begin.

The mucociliary transport system appears to consist of two main components: the mucus and the cilia. The ciliary motion is characterized by its pattern, its beat frequency, and its synchronization. So far, only the beat frequency can be studied by objective means. Means for assessing the pattern of motion and the extent of synchrony among the moving cilia are badly needed. In samples from patients with the ciliary dyskinesia syndrome a "dyskinetic" motion has been observed, but only subjective descriptions are as yet available.[8] A method recently developed by Gheber and Priel[23] to assess synchronization among beating cilia has not been applied yet in clinical material.

In vitro mucociliary clearance rates of the trachea were reported to correspond in sheep with in vitro tracheal ciliary activity.[24] In vivo tracheobronchial mucociliary clearance rates were found in humans either to weakly correlate positively[25] or to be inversely related[26,27] with in vivo clearance rates of the nose. The logarithm of in vivo nasal mucus transport time significantly correlated with in vitro nasal CBF measured at 30°C.[28] On the other hand, by perhaps more sensitive methods, no direct relationship could be demonstrated between in vitro nasal CBF and tracheal mean clearance rate.[29] As nasal CBF was found to reflect in vitro ciliary activity of the trachea, further studies are required to measure nasal and tracheal in vivo clearance rates and ciliary activity with comparable techniques. Such studies will probably help to clarify the nature of the suspected compensatory mechanism coordinating nasal with tracheobronchial mucociliary clearance.

In most studies published so far age was not considered an influential factor,[4,6,8] although the possibility was suggested.[10] The present study demonstrates that age is important. Children are more prone to upper and lower respiratory tract infections than adults, who become immunized to many agents along their course of life. It is feasible that in children, who are under a heavier immunologic load, compensating defense systems such as the mucociliary system work more vigorously, as might be reflected by a higher in vitro CBF. We are not aware of human or animal studies comparing mucociliary clearance rates between youngsters and adults, but in adults above the age of 21 years a decreased pulmonary mucociliary clearance was reported in the older patients, with a significant negative correlation between age and clearance rates.[30] At this point it is obvious that the age of the control subjects should be considered and matched in any study involving in vitro CBF determinations.

Gender was not shown previously to affect pulmonary or nasal mucociliary clearance.[31-33] In the present study gender did not influence in vitro nasal CBF. Since hormones have been shown to change ciliary activity in controlled laboratory studies,[34] it is possible that the test is not sensitive enough to detect the hormonal differences.

In vivo clearance studies suggest a possible genetic influence on CBF.[35] Our crude genetic marker was the ethnic origin of the subjects. While no difference was found between the two ethnic groups, each of them is rather heterogeneous.[14] Comparison of more homogeneous subpopulations may reveal more variability.

The statistically significant difference in the nasal specimens premedication and postmedication suggests that in vivo premedication with intramuscular administration of morphine sulfate (5 to 10 mg) and atropine sulfate (1 mg) and/or local application of 2 to 5 mL of a lidocaine hydrochloride 2% to 4% solution inhibits the subsequently measured in vitro CBF of nasal epithelial cells, although the effect was small. It is generally accepted that topical application of lidocaine at conventionally used concentrations (1% to 5%) does not significantly affect ciliary motion or mucociliary clearance rates, either in vitro or in vivo, in animals and humans alike.[3] It has been shown in humans that 4% lidocaine solution administered nasally in clinical doses did not affect the CBF subsequently measured in vitro.[36] Similar findings were reported in chicken tracheal rings.[37] Morphine and atropine, on the other hand, are known to decrease in vivo mucociliary clearance.[3,38] There is no information, however, as to whether such an effect persists in subsequent in vitro CBF measurements. It is possible that these exogenous agents either directly or indirectly affect the ciliated epithelium and eventually change the beat frequency even after the tissue is separated from the organism.

Patient 16 demonstrated a marked change in the CBF after the premedication and the local anesthesia both in the one available measurement of the nose and in the trachea, probably reflecting hyperreactivity to the pharmacologic agents. This is supported by a systemic reaction that this patient developed soon after the FOB examination consisting of weakness, nausea, and vomiting followed by rapid recovery. Such an effect is known in patients undergoing FOB and it is usually attributed to local anesthetic toxicity or to an idiosyncratic drug response.[39,40] Such a reaction was not observed in any of the other patients.

The elongated, probably degenerative cells that were observed in all samples are most likely a reflection of the ciliocytophthoria cytologic phenomenon.[41,42] This phenomenon, once believed to be related to viral infections, has never been studied with relation to ciliary activity. As such cells were found in normal asymptomatic as well as in sick subjects without differences, the relationship of ciliocytophthoria to infection merits a review.

ACKNOWLEDGMENTS — We thank Professor A. Silberberg for the provision of research facilities and constructive criticism. The generous help and encouragement by Drs Y. Kimhi, Z. Kam, E. Hershko, and S. Margaliot and by P. Yaron is gratefully acknowledged.

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EARLY BIOCHEMICAL EVENTS IN PNEUMOCOCCAL OTITIS MEDIA: ARACHIDONIC ACID METABOLITES IN MIDDLE EAR FLUID

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The concentrations of four arachidonic acid metabolites, prostaglandin E2, 6-keto-prostaglandin F1α, leukotriene B4, and leukotriene C4, were measured in middle ear fluid of chinchillas 6 to 72 hours after middle ear inoculation of log-phase, heat-killed encapsulated *Streptococcus pneumoniae* organisms. Compared with saline-inoculated ears, significant increases in the mean concentrations of all four metabolites were observed in the pneumococcus-inoculated ears 24 hours after inoculation, but not after 6, 48, or 72 hours. Since pneumococcus inoculation caused an influx of inflammatory cells as early as 6 hours after inoculation, before the increase in arachidonate metabolites, the initial stimulus for inflammatory cell chemotaxis is probably not metabolic products of arachidonic acid such as leukotriene B4. These metabolites may, however, amplify the subsequent inflammatory response.

KEY WORDS — arachidonic acid metabolites, inflammation, leukotrienes, otitis media, prostaglandins, *Streptococcus pneumoniae*.

INTRODUCTION

Arachidonic acid metabolites appear to be important contributors to otitis media pathogenesis. These metabolites of cell membrane phospholipid have been detected in the middle ear fluid (MEF) of patients with chronic otitis media with effusion (OME), in the MEF of chinchillas with experimental acute otitis media induced by *Streptococcus pneumoniae*, and in the MEF of chinchillas with chronic serous OME induced by eustachian tube obstruction.[1,2] We have reported that the inflammatory events of pneumococcal otitis media are associated with the cell wall of this organism.[3,4] Nonreplicating *S pneumoniae* organisms with or without capsular polysaccharide induce inflammatory cell influx, lysozyme release, and serum protein transudation into the middle ear within 6 hours after inoculation of the bacterial cells. These are the earliest cellular and biochemical responses heretofore reported in pneumococcal otitis media. The present experiment was designed to investigate the contribution and longitudinal changes of arachidonic acid metabolites during the initial phase of middle ear inflammation caused by pneumococcus.

MATERIALS AND METHODS

A total of 33 healthy 1- to 2-year-old chinchillas weighing 400 to 600 g, with normal middle ears as ascertained by otoscopy and tympanometry, were used for these experiments. The chinchilla animal model and method for preparing the inoculum have been reported.[4] Encapsulated type 7F *S pneumoniae* organisms (American type 51) were grown to log-phase, heat-killed in a boiling water bath, and adjusted to a concentration of 2 x 10^8 cells in phosphate-buffered saline (PBS) pH 7.4. Eustachian tube obstruction with Silastic sponge was performed less than 24 hours before inoculation. Bacteria were inoculated into the right middle ear hypotympanic bulla by passing a sterile catheter (Intramedic polyethylene tubing; inner diameter, 0.58 mm; outer diameter, 0.965 mm; Clay Adams, Parsippany, NY) through the dorsal bulla. A 23-gauge needle was inserted simultaneously to vent the bulla. The inoculum volume was 500 μL, and the same volume of sterile PBS was inoculated into the left ear as a control. Middle ear fluid was aspirated from the hypotympanic bulla at 6, 24, 48, and 72 hours after inoculation. The total leukocyte count was determined by use of a hemocytometer, and leukocyte differentiation was performed. Remaining fluid was centrifuged and frozen for later measurement of arachidonate metabolites. Approximately 5 μL of the aspirated effusion was cultured on 5% sheep blood agar plates and incubated for 48 hours in a 10% carbon dioxide incubator for routine bacterial identification.

The concentrations of four arachidonate metabolites were measured in MEF samples: prostaglandin E2 (PGE2), 6-keto-prostaglandin F1α (6-keto-PGF1α), leukotriene B4 (LTB4), and leukotriene C4 (LTC4). The following radioimmunoassay (RIA) kits were used: Prostaglandin E2 [^{3}H] RIA Kit, 6-keto-Prostaglandin F1α [^{3}H] RIA Kit, Leukotriene

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From the University of Minnesota Otitis Media Research Center (all authors), the Departments of Otolaryngology (Nonomura, Giebink, Harada, Juhn) and Pediatrics (Giebink), School of Medicine, and the Biostatistics Division, School of Public Health (Zelterman), University of Minnesota, Minneapolis, Minnesota. Supported by grant 8P50-CD-00133 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Minnesota.

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GEOMETRIC MEAN CONCENTRATIONS OF PROSTAGLANDINS AND LEUKOTRIENES IN CHINCHILLA MIDDLE EAR FLUID AFTER MIDDLE EAR INOCULATION OF ENCAPSULATED, HEAT-KILLED *STREPTOCOCCUS PNEUMONIAE* OR STERILE SALINE

		6 hr			*24 hr*			*48 hr*			*72 hr*		
	Ear Inoculum	*GM*	*Vol*	*No.*	*GM*	*Vol*	*No.*	*GM*	*Vol*	*No.*	*GM*	*Vol*	*No.*
PGE2	Pneumo	32.6	120	13	49.7	130	14	50.8	117	13	52.7	155	7
	Saline	42.4	126		32.2	146		40.8	96		43.7	83	
6-keto-PGF1α	Pneumo	4.9	120	13	15.8	130	14	9.0	117	13	10.0	155	7
	Saline	7.1	126		5.9	146		8.2	96		10.9	83	
LTB4	Pneumo	2.0	120	13	4.0	130	14	4.7	117	13	5.9	155	7
	Saline	3.1	126		1.8	146		3.2	96		5.7	83	
LTC4	Pneumo	0.8	120	13	2.4	133	13	1.5	120	7	6.2	164	5
	Saline	0.7	126		0.5	150		1.5	96		3.9	82	

PGE2 — prostaglandin E2, 6-keto-PGF1α — 6-keto-prostaglandin F1α, LTB4 — leukotriene B4, LTC4 — leukotriene C4, Pneumo — pneumococcus, GM — geometric mean concentration in nanograms per milliliter, Vol — mean middle ear fluid volume in microliters, No. — number of pairs of ears.

B4 [^{3}H] RIA Kit from Advanced Magnetics, Inc, Cambridge, Mass, and Leukotriene C4 [^{3}H] RIA Kit from E. I. du Pont de Nemours & Co, Boston, Mass. Assays were performed by ethanol extraction. To each 10-μL sample was added 200 μL of ethanol, followed by a 30-minute incubation at room temperature in the dark. Samples were centrifuged, and the supernatant was dried under nitrogen. One milliliter of 5% ethanol was added, and the sample was applied to a conditioned 1-mL C-18 disposable column (J. T. Baker Research Products, Phillipsburg, NJ). The column was washed with 4 mL of water, and the metabolites were collected in 10 mL of methanol effluent. Methanol was evaporated, and the sample was dissolved in 1 mL of assay buffer and stored at −70°. Each sample was assayed in duplicate. Specificities of the four assays are as follows: with the PGE2 kit, PGE2 is 100%, PGE1 is 50%, and 6-keto PGF1α, LTB4, and LTC4 are less than 1%; with the 6-keto-PGF1α kit, 6-keto-PGF1α is 100% and PGE2 is 0.6%; with the LTB4 kit, LTB4 is 100% and PGE2, 6-keto-PGF1α, and LTC4 are less than 1%; with the LTC4 kit, LTC4 is 100%, LTD4 is 55%, LTB4 is 0.06%, and PGE2 and 6-keto-PGF1α are insignificant. Differences among kit lots were adjusted by internal control.

Data were analyzed by a two-tailed, paired *t* test after log transformation of the data. Only data from chinchillas whose MEF remained sterile throughout the study were included in the analysis. Ears with tympanic membrane perforation or bleeding during paracentesis of fluid and ears with less than 60 μL fluid aspirated were excluded from analysis; therefore, the number of ears analyzed at each time point varied (see Table).

RESULTS

Data from 3 of the 33 chinchillas entering the study were excluded because of contaminating middle ear infection, leaving data from 30 animals for analysis. Significant MEF inflammatory cell influx was observed in *S pneumoniae*-inoculated ears between 6 and 72 hours after inoculation ($p<.01$ at all sampling times; see Figure, A), as we have reported.[4]

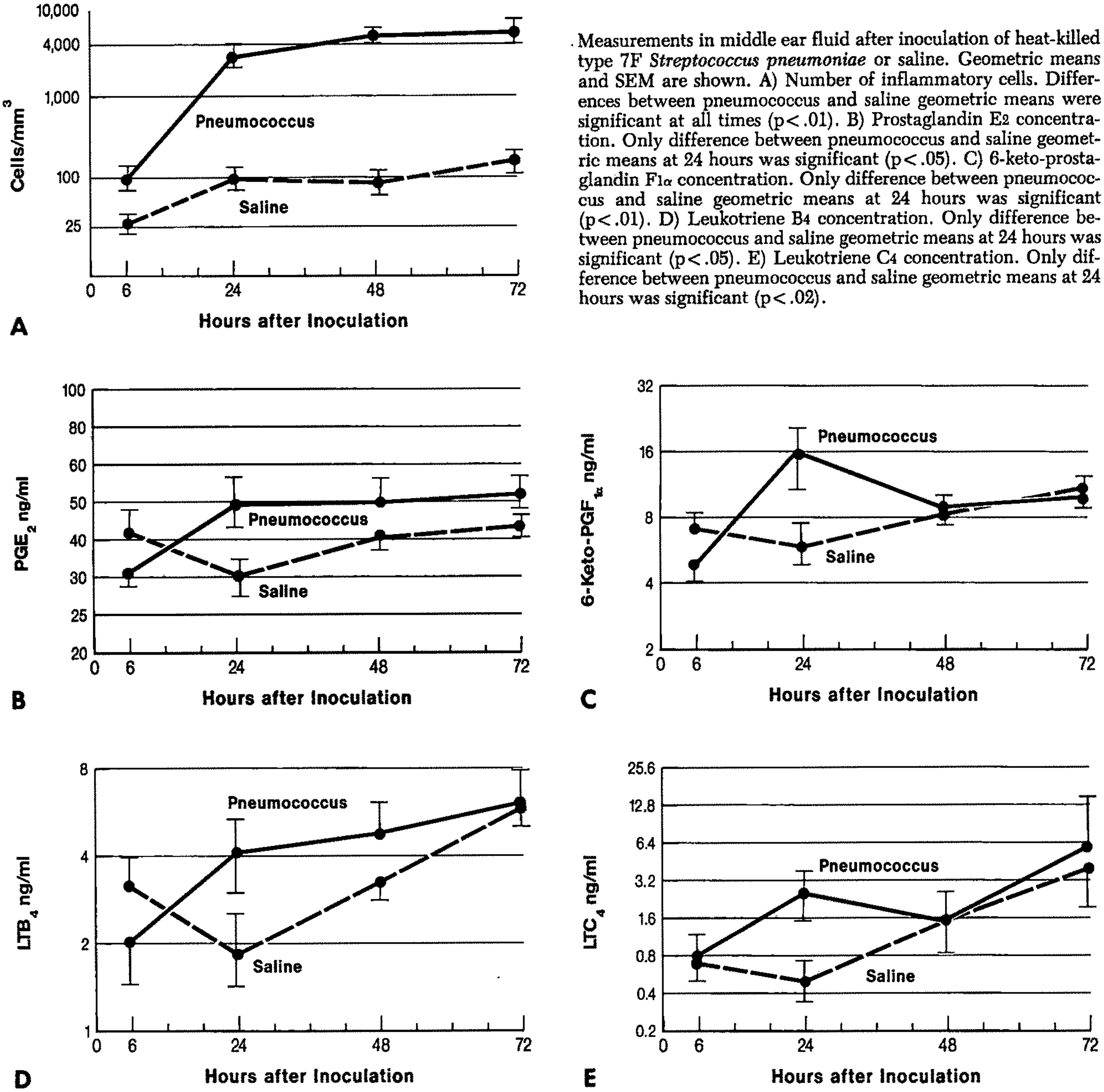
The geometric mean concentrations of PGE2 and 6-keto-PGF1α were higher in pneumococcus-inoculated ears than in saline-inoculated ears between 24 and 72 hours after inoculation; however, only the differences at 24 hours were significant (for PGE2, 49.7 versus 32.2 ng/mL, $p<.05$; for 6-keto-PGF1α, 15.8 versus 5.9 ng/mL, $p<.01$; see Table and Figure; B,C).

The geometric mean concentrations of LTB4 and LTC4 also were higher in pneumococcus-inoculated ears than in saline-inoculated ears between 24 and 72 hours after inoculation; however, only the differences at 24 hours were significant (for LTB4, 4.0 versus 1.8 ng/mL, $p<.05$; for LTC4, 2.4 versus 0.5 ng/mL, $p<.02$; see Table and Figure; D,E).

DISCUSSION

Arachidonic acid metabolites, which are derived from cell membrane phospholipids of many mammalian cells, are present in inflammatory tissues, including the middle ear space in otitis media.[1] This experiment demonstrated that *S pneumoniae*, the most common pathogen in acute otitis media, triggers arachidonic acid metabolism in the middle ear to both prostaglandin and leukotriene products; their concentrations in pneumococcus-inoculated ears significantly exceeded those in control ears that had only eustachian tube obstruction. Heat-killed rather than living organisms were used to enable measurement of inflammatory response kinetics and relationships among the inflammatory mediators. Under these conditions, the increase in prostaglandin and leukotriene products, which was first apparent 24 hours after inoculation, followed the influx of inflammatory cells, which began before 6 hours, suggesting that the arachidonate products were derived from inflammatory cells. Since the generation time of *S pneumoniae* is 10 to 20 minutes, these events would most likely be accelerated considerably in an active pneumococcal middle ear infection.

Arachidonic acid is metabolized by the action of two enzymes, cyclooxygenase and lipoxygenase.[5] Prostaglandins and thromboxane are formed by the



Measurements in middle ear fluid after inoculation of heat-killed type 7F *Streptococcus pneumoniae* or saline. Geometric means and SEM are shown. A) Number of inflammatory cells. Differences between pneumococcus and saline geometric means were significant at all times ($p<.01$). B) Prostaglandin E2 concentration. Only difference between pneumococcus and saline geometric means at 24 hours was significant ($p<.05$). C) 6-keto-prostaglandin F1α concentration. Only difference between pneumococcus and saline geometric means at 24 hours was significant ($p<.01$). D) Leukotriene B4 concentration. Only difference between pneumococcus and saline geometric means at 24 hours was significant ($p<.05$). E) Leukotriene C4 concentration. Only difference between pneumococcus and saline geometric means at 24 hours was significant ($p<.02$).

action of cyclooxygenase, and PGE2 and prostaglandin I2 (PGI2) are probably the most important products of this enzyme during inflammation.[6] Both PGE2 and PGI2 are synthesized by mononuclear and polymorphonuclear leukocytes. Prostaglandin I2, of which 6-keto-PGF1α is the end product, is also synthesized by arterial endothelial cells. Chinchilla middle ear mucoperiosteum cultured in vitro has been shown to produce PGE2 and 6-keto-PGF1α after arachidonic acid was added to the culture medium; this finding indicates that mucoperiosteal cells in the absence of host inflammatory cells and vascular endothelium can synthesize these prostaglandins (T. Harada, unpublished observations, 1989). This evidence, taken with the delayed increase in arachidonic acid metabolites after the initial influx of inflammatory cells in pneumococcus-inoculated ears, suggests that another source of prostaglandin products during the early phase of pneumococcus-initiated middle ear inflammation may be mucoperiosteal epithelium. Confirmatory immunohistochemical experiments are planned.

Several lines of evidence indicate that arachidonic acid metabolites contribute to the pathogenesis of middle ear inflammation. Both prostaglandin and leukotriene products have been detected in MEF samples from patients with chronic OME and from chinchillas with experimental purulent and serous otitis media induced by *S pneumoniae* and eustachian tube obstruction, respectively.[1,2] Repetitive inoculation of PGE2, LTC4, and arachidonic acid alone or in combination caused middle ear inflammation in chinchillas in another study.[7] Moreover, chinchilla middle ear mucosa can synthesize all of the prostaglandin products from arachidonic acid injected into the middle ear cavity of chinchillas with eustachian tube obstruction.[2]

The biologic activities of PGE2 include vascular dilatation, increased vascular permeability, and pyrogenicity.[7] Prostaglandin I2 increases capillary flow, causes hyperalgesia, inhibits platelet aggregation, and may modulate the production of surface active agents.[7,8] The increase in these prostaglandins and LTC4, which also causes plasma leakage, 24 hours after pneumococcus inoculation is consistent with serum protein transudation into MEF, which has been reported.[4] Because albumin and α2-macroglobulin concentrations in MEF were significantly increased above those in saline-inoculated ears 6 hours after inoculation, mediators other than arachidonic acid metabolites probably contribute to increased vascular permeability in the early phase of middle ear inflammation. The increase of 6-keto-PGF1α in ears inoculated with nonviable pneumococcus suggests that the bacterial cell envelope has a direct effect on vascular endothelium in the mucoperiosteum.

Leukotrienes and hydroxyeicosatetraenoic acid are produced by the action of lipoxygenase. Leukotriene C4 causes arteriolar construction and plasma leakage from postcapillary venules.[9] Leukotriene B4, which is synthesized by polymorphonuclear leukocytes and macrophages, is a strong inflammatory mediator with potent chemotactic and degranulating activities on neutrophil function.[10] Since significant inflammatory cell influx into middle ear effusion was observed 18 hours before a significant increase in LTB4 could be measured, the chemotaxin for these cells was another substance, probably the pneumococcal cell, which has potent chemotactic activity.[11] However, LTB4 synthesized by these inflammatory cells may have served as a chemotactic stimulus for subsequent neutrophil influx. This conclusion is consistent with our earlier observation in children with chronic OME, in whom there was a low correlation between MEF chemotactic activity and the MEF concentration of the chemotactic serum complement protein C5a.[12]

In summary, encapsulated *S pneumoniae* in the chinchilla middle ear causes arachidonic acid synthesis and enzymatic breakdown into prostaglandin and leukotriene products. These products most likely amplify the inflammatory response. The failure of corticosteroid treatment to produce long-lasting resolution of chronic OME may be explained by this apparent secondary role of arachidonate metabolites in pneumococcal otitis media.[13-16] Therefore, therapeutic interventions that enhance the early clearance of bacterial cells during middle ear inflammation may prevent the development of chronic OME and the resulting pathologic changes characteristic of chronic intractable otitis media.

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ALTERED EFFECT OF ARACHIDONIC ACID ON INNER EAR BLOOD FLOW IN RATS WITH STREPTOZOTOCIN-INDUCED DIABETES

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The present study was undertaken to clarify the altered effect of arachidonic acid on inner ear blood flow in rats with streptozotocin-induced diabetes by use of the laser-Doppler flowmeter. Drugs were administered intraarterially via the subclavian artery in a dose range that did not affect the systemic blood pressure. Both arachidonic acid and papaverine hydrochloride increased inner ear blood flow dose-dependently. Diabetic rats at 12 weeks, but not at 8 weeks, after the induction of diabetes showed a significant decrease in arachidonic acid response. However, there were no differences in papaverine response between diabetic and control rats. Pretreatment with ONO-3708, a selective thromboxane A2 antagonist, reversed the attenuated response to arachidonic acid found in diabetic rats. An increased response to thromboxane A2, which decreased inner ear blood flow, was also found in 12-week diabetic rats. In electrocochleograms, the latency in 12-week diabetic rats was significantly delayed compared with that in control rats, and this prolonged latency improved with insulin treatment. These results suggest that the responsiveness of inner ear blood flow to prostaglandins may be altered in individuals with diabetes mellitus.

KEY WORDS — diabetic hearing disorders, inner ear microcirculation, prostaglandins.

INTRODUCTION

It is well known that diabetes mellitus causes microangiopathy and neuropathy in all tissues and organs. Diabetes mellitus has been reported to be accompanied by sensorineural hearing loss[1-4] since Jardao[5] reported one case of hearing disorder with diabetes mellitus. The histologic studies of temporal bones of human diabetics[6-8] and experimental animals[9,10] show changes in the small blood vessels of the stria vascularis and the modiolus. Jorgensen[11] studied the temporal bones of 32 diabetic patients and showed severe periodic acid–Schiff stain–positive thickening of the capillary walls of the stria vascularis. These findings suggested that hearing disorders of diabetes mellitus were caused mainly by microangiopathy.

Recent evidence has suggested that prostaglandins (PGs) and the related thromboxanes represent an important regulatory system modulating the interaction of platelets and blood vessels.[12] In the inner ear, the synthesis of PGs was also reported in guinea pigs.[13,14] In our previous study,[15] we found that arachidonic acid, a precursor of PGs, caused an increase in rat inner ear blood flow and that PGs were considered to play an important role in regulating inner ear blood flow. In diabetic patients and experimental models, both disturbed vascular function and increased platelet aggregation[16,17] were observed, and these alterations could be explained by abnormal metabolism of arachidonic acid, namely an increased formation of thromboxane A2 (TXA2) by the platelets and/or a decreased synthesis of prostacyclin by the vessel wall.[18] From these findings, it was considered that the altered metabolism of arachidonic acid may also occur in the inner ear in diabetes mellitus; this altered metabolism would be associated with microangiopathy and hearing disorders.

The purpose of this study was to investigate the effect of arachidonic acid on the inner ear blood flow of rats with streptozotocin (STZ)–induced diabetes.

MATERIALS AND METHODS

Experimental Animals. Diabetes was induced in 47 male Wistar rats (10 weeks old) by intravenous injection of STZ (Sigma) at a dose of 35 mg/kg body weight. Diabetic animals were used at 8 and 12 weeks after the injection of STZ. Twenty-one nondiabetic rats were used as controls. Blood collected at the end of experimentation was used for serum glucose determinations by the mutarotase -D-glucose oxidase method.[19] In 10 animals, insulin was administered at a dose of 4 U/d subcutaneously for 4 weeks, starting 8 weeks after the injection of STZ. The serum glucose levels and body weights are shown in Table 1.

Animal Preparation. The use of a laser-Doppler flowmeter for measurement of inner ear blood flow has been described in detail previously.[15] In brief, all rats, which were confirmed to have normal Preyer's reflex, were anesthetized with pentobarbital sodium (50 mg/kg intraperitoneally) and artificially ventilated with a respirator (Harvard 683). Body temperature was maintained at 37°C with a heating pad. A catheter was placed in the femoral

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From the Department of Pharmacology, Hamamatsu University School of Medicine, Hamamatsu, Japan. This study was performed in accordance with the Guidelines for Animal Experiments of Hamamatsu University School of Medicine; the animal use protocol was approved by the Animal Experiments Committee of Hamamatsu University School of Medicine.

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TABLE 1. BODY WEIGHT AND BLOOD GLUCOSE LEVEL (MEAN ± SEM)

	No.	*Body Weight (g)*	*Blood Glucose Level (mg/100 mL)*
Control rats	21	240 ± 4.9	184 ± 10.2
8-week diabetic rats	11	162 ± 5.4	632 ± 34.9
12-week diabetic rats	26	147 ± 4.0	626 ± 35.5
Insulin-treated rats	10	295 ± 16.7	321 ± 12.2

TABLE 2. LATENCY OF ACTION POTENTIALS IN ELECTROCOCHLEOGRAMS (MILLISECONDS, MEAN ± SEM)

	Control Rats (n = 5)	*8-Week Diabetic Rats (n = 5)*	*12-Week Diabetic Rats (n = 5)*	*Insulin-treated Rats (n = 5)*
85 dB SPL	1.12 ± 0.01	1.16 ± 0.01	1.20 ± 0.02*	1.12 ± 0.01§
80 dB SPL	1.17 ± 0.02	1.21 ± 0.02	1.23 ± 0.02†	1.14 ± 0.01§
75 dB SPL	1.20 ± 0.01	1.23 ± 0.01	1.26 ± 0.01†	1.16 ± 0.01§

Stimuli consist of 8-kHz sine waves.
SPL — sound pressure level.
*$p < .01$ versus control rats.
†$p < .05$ versus control rats.
§$p < .001$ versus 12-week diabetic rats.

artery and connected to a pressure transducer (Nihon-Kohden, MPU-05, RP-5). Another catheter for drug administration was inserted at the subclavian artery and guided to the vertebral artery. In a preliminary experiment, the location of the catheter was verified by angiography with radiopaque dyes that were injected into the catheter. The middle ears were approached ventrally and the bulla was opened without disturbing the ossicles or tympanic membrane. The middle ear was judged normal by direct visualization. A laser-Doppler probe (ALF 2100 Advance, Japan; diameter, 1 mm) was positioned on the basal turn of the cochlea after the overlying mucosa was removed with cotton pledgets. The blood flow and systemic blood pressure were recorded on a pen recorder (Rikaden, R-16).

Drugs and Experimental Protocol. The following drugs were used: sodium arachidonate (Sigma) 20 to 50 μg; 9,11-epithio-11,12-methano-thromboxane A2 (STA2), a stable thromboxane A2 analogue (ONO), 30 to 80 ng; papaverine hydrochloride (Sigma) 2 to 10 μg; and (9,11),(11,12)-dideoxa-9α,11α-dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14oxo-15cyclopentyl-16,17,18,19,20-pentanor-15-epi-thromboxane A2 (ONO-3708), a selective thromboxane A2 antagonist.[20] The pH was adjusted between 7 and 8 in all drug solutions. The dosage of each drug was adjusted so as not to affect systemic blood pressure.

After an equilibration period of 20 minutes, each drug was injected intraarterially at the rate for injection of a 100-μL volume. Dose-response curves were performed noncumulatively every 20 minutes. Each drug was administered in order of increasing dose.

In order to assess TXA2 antagonist effect, arachidonic acid was injected intraarterially before the infusion of TXA2 antagonist ONO-3708. After continuous infusion of a TXA2 antagonist at the rate of 10 μg/kg per minute via the femoral vein for a period of 30 minutes, arachidonic acid was injected intraarterially in the same diabetic rat.

Electrocochleograms were recorded with the Neuro-Pack II (Nihon-Kohden, Japan) as an index of hearing disorders. The animals were anesthetized with pentobarbital sodium (50 mg/kg intraperitoneally). The bulla was approached ventrally and opened. A silver ball electrode (an active electrode) was placed on a round window. An indifferent electrode was placed in muscle near the bulla. The eardrum was directly observed by cutting across the external meatus. The stimuli (in decibels sound pressure level) were 8-kHz sine waves at 0.2-millisecond durations and 75-millisecond intervals (DA-502ARM, DANA Japan). An earphone (TDH-49, Telephonics, USA) was attached by open field to the external meatus and sound calibration was accomplished by microphone (NA-09, Rion, Japan) at the eardrum. The latency and threshold of action potentials were measured.

Presentation and Analysis of Results. Results (Tables 1-3 and Figs 1-5) were expressed as the mean ± SEM. Blood flow data are presented as percent change from the baseline. Data were statistically analyzed with Student's *t* test when only two groups were involved. Comparison of more than two groups was performed by analysis of variance followed by Dunnett's test.

RESULTS

Arachidonic Acid. Arachidonic acid caused an increase in inner ear blood flow in a dose-dependent manner without changing the systemic pressure. Figure 1 presents dose-response curves for the effect of arachidonic acid on inner ear blood flow in diabetic rats at 8 and 12 weeks after the induction of diabetes, in insulin-treated rats, and in control rats. No significant differences were observed between the responses in 8-week diabetic rats and the control rats. On the other hand, the responses in 12-week diabetic rats were decreased, especially at the highest dose, compared to those in control rats. Insulin reversed the attenuated effect of arachidonic acid on inner ear blood flow in 12-week diabetic rats.

TABLE 3. THRESHOLD OF ACTION POTENTIALS ON ELECTROCOCHLEOGRAMS (MEAN ± SEM)

	No.	*Threshold (dB SPL)*
Control rats	5	38.0 ± 4.1
8-week diabetic rats	5	35.0 ± 3.7
12-week diabetic rats	5	36.0 ± 4.0
Insulin-treated rats	5	30.0 ± 2.7

Stimuli consist of 8-kHz sine waves.
SPL — sound pressure level.

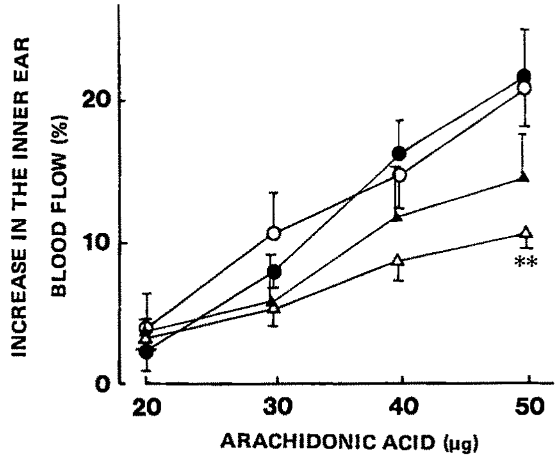

Fig 1. Effect of arachidonic acid on inner ear blood flow. Arachidonic acid was administered intraarterially via subclavian artery. Values are presented as percent change from baseline. Each point represents mean ± SEM. Filled circles — control rats (n = 7), empty circles — 8-week diabetic rats (n = 6), empty triangles — 12-week diabetic rats (n = 6), filled triangles — insulin-treated rats (n = 5), ** — $p < .01$ versus control rats.

STA2. STA2, a stable TXA2 analogue, caused a decrease in inner ear blood flow in a dose-dependent manner without altering systemic blood flow. Dose-response curves in 12-week diabetic rats and control rats are shown in Fig 2. STA2 decreased inner ear blood flow significantly in 12-week diabetic rats compared to control rats. Insulin reversed the attenuated effect of STA2 on inner ear blood flow in 12-week diabetic rats.

TXA2 Antagonist ONO-3708. A TXA2 antagonist, ONO-3708, abolished the exogenous STA2 response at a dose of 10 μg/kg per minute. ONO-3708 did not affect the response to arachidonic acid in four control rats (Fig 3). However, ONO-3708 reversed the attenuated effect of arachidonic acid on inner ear blood flow in 12-week diabetic rats (Fig 4).

Papaverine. Papaverine caused an increase in inner ear blood flow in a dose-dependent manner. No significant differences in the response to papaverine were observed between the diabetic and the control groups (Fig 5).

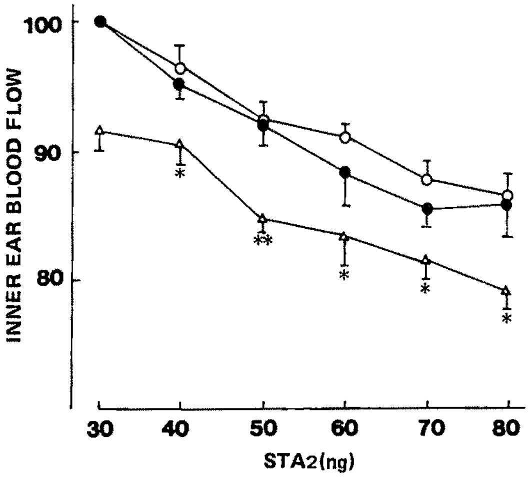

Fig 2. Effect of STA2 on inner ear blood flow. STA2 was administered intraarterially via subclavian artery. Values are presented as percent change from baseline. Each point represents mean ± SEM. Empty circles — control rats (n = 5), triangles — 12-week diabetic rats (n = 5), filled circles — insulin-treated rats (n = 5), ** — $p < .01$ versus control rats, * — $p < .05$ versus control rats.

Electrocochleography. The latency of action potentials is shown in Table 2. The latency of action potentials in 12-week diabetic rats was significantly delayed, but not in 8-week diabetic rats, compared to that in control rats. Insulin treatment improved the latency of the action potentials in diabetic rats.

The threshold of action potentials is shown in Table 3. No significant differences were observed among 8-week diabetic and 12-week diabetic rats, normal rats, and insulin-treated diabetic rats.

DISCUSSION

Prostaglandins are synthesized in all tissues and

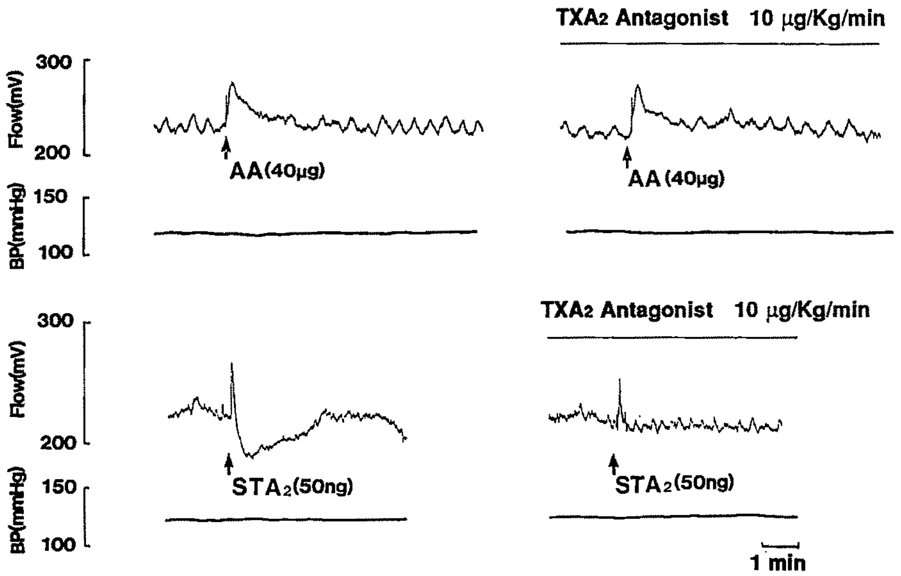

Fig 3. Typical tracing of effect of antagonist of thromboxane A2 (TXA2), ONO-3708, on control rats. Arachidonic acid (AA) or STA2 was administered intraarterially via subclavian artery before or after infusion of ONO-3708. Flow — inner ear blood flow, BP — mean blood pressure.

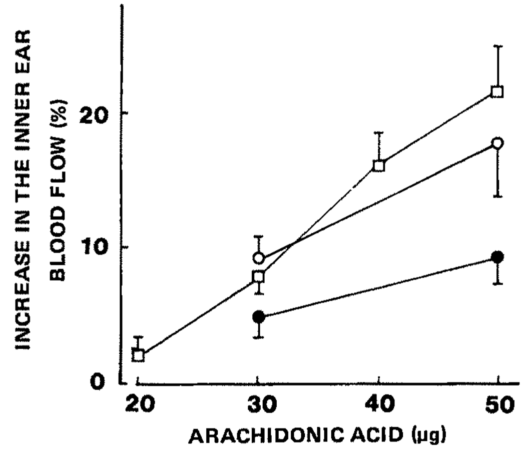

Fig 4. Effect of antagonist of thromboxane A2 (TXA2), ONO-3708, on 12-week diabetic rats. Arachidonic acid was injected intraarterially before infusion of ONO-3708. After continuous infusion of this TXA2 antagonist at rate of 10 µg/kg per minute via femoral vein for period of 30 minutes, arachidonic acid was injected intraarterially in same diabetic rat. Values are presented as percent change from baseline. Each point represents mean ± SEM (n = 5). Squares — effect of arachidonic acid in control rats, filled circles — effect of arachidonic acid before infusion of ONO-3708, empty circle — effect of arachidonic acid after infusion of ONO-3708.

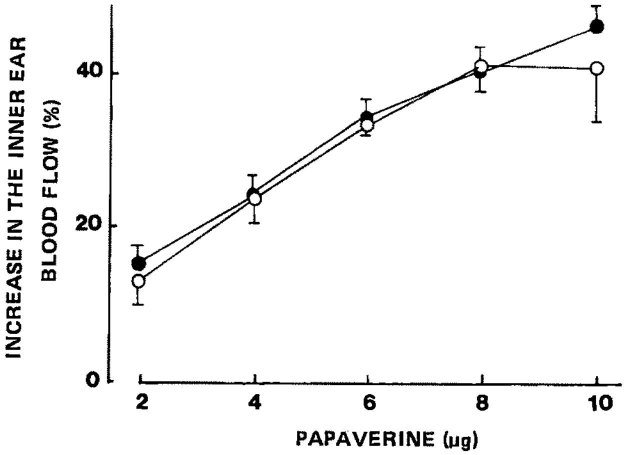

Fig 5. Effect of papaverine hydrochloride on inner ear blood flow. Papaverine was administered intraarterially via subclavian artery. Values are presented as percent change from baseline. Each point represents mean ± SEM. Filled circles — control rats (n = 5), empty circles — 12-week diabetic rats (n = 5).

organs, and they regulate microcirculation. In the inner ear, also, the synthesis of PGs has been reported.[13,14] In the previous study,[15] we found that arachidonic acid increased inner ear blood flow in rats. That this response was abolished by indomethacin indicates that some PGs are involved in the effect of arachidonic acid on inner ear blood flow. Prostaglandin E2 (PGE2) and prostacyclin increased inner ear blood flow, and TXA2 decreased it. Prostaglandin F2α caused no change in it. From these findings, we considered that PGs could be humoral mediators of the homeostasis of inner ear circulation and that PGE2 and prostacyclin may mainly regulate inner ear blood flow.

Both disturbed vascular function and increased platelet aggregation were observed in diabetic patients,[16,17] and they could be explained by increased formation of TXA2 by the platelets and/or decreased synthesis of prostacyclin by the vessel wall.[18] Roth et al[21] reported that responsiveness to TXA2 increased in diabetic rat aortas. In our study, the response to arachidonic acid of inner ear blood flow was decreased in 12-week diabetic rats compared with control rats (Fig 1). This response to arachidonic acid was not influenced by a TXA2 antagonist in the control rats, whereas the altered response to arachidonic acid found in 12-week diabetic rats was improved by a TXA2 antagonist. Thromboxane A2 decreased inner ear blood flow, and the response to TXA2 was significantly increased in 12-week diabetic rats. Insulin reversed the attenuating effect of arachidonic acid and TXA2 on inner ear blood flow in 12-week diabetic rats. Papaverine, a nonspecific vasodilator, increased inner ear blood flow in a dose-dependent manner, the same as arachidonic acid. However, there were no significant differences in the response to papaverine between 12-week diabetic rats and control rats. The effect of papaverine was not changed, and the effect of arachidonic acid was altered. Therefore, the attenuating effect of arachidonic acid in 12-week diabetic rats appears to result from increases in the generation of and/or vascular reactivity to TXA2.

In electrocochleograms, the latency of action potentials in 12-week diabetic rats was delayed significantly compared with that in control rats, whereas the threshold of action potentials in 12-week diabetic rats was the same as that in control rats. The delayed latency was recovered to normal with insulin treatment. The impairment shown by electrocochleogram may be caused by diabetes. The altered response shown by electrocochleogram 12 weeks after induction of diabetes occurred at the same time as did the altered response to arachidonic acid. These results suggest that the responsiveness of inner ear blood flow to PGs may be altered in individuals with diabetes mellitus.

ACKNOWLEDGMENT — We are indebted to ONO Pharmaceutical Co, Ltd, for supplying 9,11-epithio-11,12-methano-TXA2 and (9,11),(11,12)-dideoxa-9α,11α-dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14oxo-15cyclopentyl-16,17,18,19,20-pentanor-15-epi-TXA2 (ONO-3708).

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Ann Otol Rhinol Laryngol 100:1991

COCHLEAR BLOOD FLOW UNDER INCREASED INNER EAR PRESSURE

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The effect of elevation of inner ear pressure on cochlear blood flow in guinea pigs was studied with use of nonradioactive microspheres and a laser-Doppler flowmeter. Hydrostatic pressure was applied to the perilymph through a glass capillary tube inserted into the scala tympani of the basal turn. Because of the elevation of the inner ear pressure, the cochlear blood flow, except to the modiolus, decreased significantly. Above all, the blood flow in the capillaries or microcirculation in the cochlea was most easily impaired by the elevation of inner ear pressure.

KEY WORDS — cochlear blood flow, inner ear pressure, microcirculation.

Our previous studies[1,2] showed that increased inner ear pressure compressed the cochlear blood vessels and reduced cochlear blood flow (CBF). When the inner ear pressure was elevated sufficiently, the endolymphatic potential (EP), which is sensitive to the lack of oxygen, decreased as in response to anoxia. However, it has not been proved that this situation occurs clinically, wherein raised inner ear pressure causes a decrease in CBF.

Although it has been recognized clinically that increased cerebrospinal fluid (CSF) pressure impairs cerebral blood flow[3,4] and increased intraocular pressure impairs retinal blood flow,[5,6] the effect of an elevated inner ear pressure on CBF remains speculative in inner ear disorders.[1,7] Even in experimental studies on animals, the relationship between an elevated inner ear pressure and CBF is largely unclear. We therefore attempted to study the susceptibility of the vessels in various sites of the cochlea to an elevation in inner ear pressure.

METHODS

Sixteen guinea pigs weighing 200 to 350 g were anesthetized with either intraperitoneal ethyl carbamate (Urethane, 1.5 to 2.0 g/kg) or pentobarbital sodium (Nembutal, 30 to 40 mg/kg). Tracheostomy was performed, and the animals were paralyzed with succinylcholine chloride. Their pulmonary ventilation was performed with an artificial respirator throughout the experiment. In 14 animals, the tympanic bulla was opened and the cochlea exposed ipsilaterally. In 13 animals, the bony wall of the scala tympani of the basal turn was drilled successfully and a glass capillary tube with a tip diameter of 200 to 300 μm was inserted into the perilymph and fixed to the bone with dental cement to prevent leakage. The glass capillary tube was connected by a catheter and a three-way tap to a pressure transducer, with the third outlet of the tap communicating with a saline reservoir. The perilymphatic pressure could be altered by raising or lowering the reservoir, and the pressure was recorded continuously.

When the inner ear pressure was raised, CBF was recorded by a laser-Doppler flowmeter (Advance, ALF 2100) in 11 animals and EP was measured in 2 animals. The laser-Doppler flowmeter has a needle probe (outer diameter, 1.0 mm) and the tip of the probe was placed on the bony wall of the basal turn or second turn after removing the middle ear mucosa overlying the cochlea. Although this laser-Doppler flowmeter shows the flow in milliliters per 100 g per minute, the absolute amount as such is meaningless in measurements of CBF and instead this measure is considered as a scale of relative change. Blood pressure was measured simultaneously through a catheter inserted into the carotid artery in 6 of 11 animals in which the CBF was recorded by the laser-Doppler flowmeter. The catheter was connected by a tube that contained saline and heparin to a pressure transducer (Toyoda, PMS-5M-0.5H) and amplifier (Toyoda, AA3000). Two similar pressure transducers and amplifiers were used to record the blood pressure and perilymphatic pressure simultaneously. The EP was recorded by inserting a glass microelectrode into the endolymphatic space through the round window membrane and the basilar membrane after a part of the tympanic membrane was removed. The microelectrode was filled with 2 mol/L potassium chloride solution and connected to an amplifier (WPI model 900). In this experiment, endolymphatic pressure was not measured.

The distribution of the CBF was studied with nonradioactive microspheres. Nonradioactive microspheres of 9.03 ± 1.03 μm in diameter, suspended

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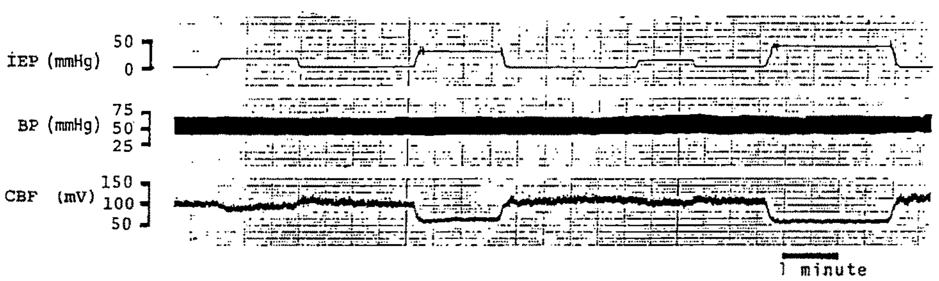

Effect of changes of inner ear pressure (IEP) on cochlear blood flow (CBF). Blood pressure (BP) did not change significantly, but CBF decreased because of elevation of IEP. In this figure, IEP is raised four times. CBF is shown in degree of output (mV) of laser-Doppler flowmeter.

in 1.0 to 2.0 mL saline, were injected into the left ventricle within about 1 minute after thoracotomy was performed. In 4 of 12 animals in which the inner ear pressure was successfully manipulated, the microspheres were injected while the CBF indicated by the laser-Doppler flowmeter or the value of EP decreased following the elevation of the inner ear pressure. In 2 animals, the microspheres were injected without opening the tympanic bulla. In 1 animal, microspheres were injected even though the drilling of the basal turn was unsuccessful because of the fracture of the bony wall.

After the microspheres were injected, the animals were killed painlessly by intracardial injection of potassium chloride, and the temporal bones were removed, fixed with 2% glutaraldehyde, and decalcified in 10% ethylenediaminetetraacetic acid. Using the surface preparation technique and phase-contrast microscopy, we counted the number of microspheres trapped in the blood vessels of the cochlea, dividing the cochlea into lateral, spiral, and central portions in each cochlear turn. The lateral portion included radiating arterioles in the scala vestibuli, vessels of the spiral ligament, vessels of the stria vascularis, and vessels of the spiral prominence. The spiral portion included vessels of the basilar membrane, vessels of the tympanic lip, and vessels of the osseous spiral lamina. The central portion included the region of the modiolus. Comparison of the numbers of microspheres between the control (right) and test (left) cochleas was performed, and the distribution of the CBF was shown by the ratio of the number of microspheres present in each blood vessel to the total number of microspheres in the cochlea. The absolute amount of CBF was not measured because reference blood samples were not taken. Regarding the classification of the blood vessels in the cochlea, we followed the method described by Axelsson et al.[8]

RESULTS

The laser-Doppler flowmeter showed a reduction of CBF when the inner ear pressure was raised (see Figure). Immediately after the inner ear pressure was raised, the CBF decreased. This decrease was reversible by applications of pressure for brief periods of time. The degree of reduction of the CBF depended on the degree of elevation of the inner ear pressure. A slight reduction of the CBF occurred when the inner ear pressure was raised to 10 to 15 mm Hg, and a significant reduction of the CBF was observed when the inner ear pressure was elevated near the level of the mean arterial blood pressure. In this experiment, the systolic blood pressure of the carotid artery ranged from 35 to 80 mm Hg in different animals at the beginning of the measurement of blood pressure. The required inner ear pressure for the reduction of CBF was low in hypotensive animals. Thus, the inner ear pressure necessary to lower the CBF was related to the blood pressure, although the manipulation of inner ear pressure itself did not induce a significant change in blood pressure. The EP also decreased as in response to anoxia when the inner ear pressure was raised.

In this experiment, the microspheres were injected while the CBF or EP was low, but not at the lowest level. The number and distribution of the microspheres in each animal are shown in the Table. When the numbers of microspheres between the control (right) and test (left) cochleas were compared, the numbers of microspheres in the test cochleas ranged from 18% to 37% of that of the controls. In animal 1, which showed the least reduction of CBF due to the elevation of inner ear pressure, the blood flow of the stria vascularis and spiral prominence decreased significantly. In animal 2, in which the CBF decreased more than that in animal 1, the blood flow of the spiral ligament, the vessel of the basilar membrane, and the vessel of the tympanic lip was reduced significantly, as was the blood flow of the stria vascularis and spiral prominence. In animals 3 and 4, the CBF was impaired more strongly and the blood flow of the arterioles of the scala vestibuli and spiral lamina also decreased. These results indicated that blood flow in the capillaries or microcirculation in the cochlea was most vulnerable when the inner ear pressure was raised. In contrast, the blood flow of the modiolus was preserved and the percentage of the microspheres in the central portion increased significantly when the inner ear pressure was raised.

The distribution of microspheres was evaluated by cochlear turn. In the test cochleas in animals 1 through 4, 72.3% ± 10.1% of the microspheres were found in the basal turn including the hook, 16.5% ± 3.5% in the second turn, 9.0% ± 7.6% in the third turn, and 2.0% ± 1.2% in the apical turn. In the control cochleas in animals 1 through 4,

NUMBER AND DISTRIBUTION OF MICROSPHERES TRAPPED IN COCHLEA

			Distribution of Microspheres (%)									
			Lateral Portion						*Spiral Portion*			*Central Portion*
Animal	*Side*	*No. of Microspheres*	*RAL*	*VSVM*	*SVS*	*SP*	*SL*	*VBM*	*RAL*	*VSBM*	*VSTL*	*MO*
Hydrostatic pressure applied to left cochlea												
1	R	786	15	2	7	8	16	0	17	2	2	33
	L	291	10	1	2*	2*	9	0	20	2	3	51†
2	R	511	13	2	13	11	14	2	10	5	2	28
	L	119	12	0*	3*	1*	3*	0	5	0*	0*	76†
3	R	287	14	2	14	8	9	0	9	3	2	37
	L	52	4*	0*	0*	0*	2*	0	2*	0*	0*	92†
4	R	302	20	2	15	8	19	2	6	2	3	23
	L	99	0*	0*	0*	0*	0*	0	4*	0*	0*	96†
No hydrostatic pressure applied												
5	R	585	22	1	6	10	17	0	11	2	4	28
	L	541	20	2	8	12	18	2	15	3	3	18
6	R	257	14	1	7	8	9	1	21	4	4	31
	L	201	21	3	13	13	18	1	10	0	1	18
Fracture of external wall of left cochlea												
7	R	272	20	1	12	13	15	1	12	3	3	19
	L	187	16	2	10	6	21	1	13	3	1	28

RAL — radiating arterioles, VSVM — vessel at vestibular membrane, SVS — stria vascularis, SP — spiral prominence (vessel of spiral prominence), SL — spiral ligament (arteriovenous anastomoses), VBM — venules at basilar membrane, VSBM — vessel of basilar membrane, VSTL — vessel of tympanic lip, MO — modiolus.

*Reduction of more than 2 SD from mean of nine control ears (both ears in animals 5 and 6 and right ears in animals 1 through 4 and 7).

†Increase of more than 2 SD from mean of nine control ears.

54.8% ±7.5% of the microspheres were found in the basal turn including the hook, 24.5% ±4.2% in the second turn, 13.3% ±3.5% in the third turn, and 7.5% ±3.9% in the apical turn. The increase in microspheres with elevation of inner ear pressure was significant in the basal turn (*t* test, $p < .025$), but in the other three turns, the percentage of microspheres decreased on elevation of the inner ear pressure. Thus, the CBF decreased more strongly in the upper turns than in the basal turn following the elevation of the inner ear pressure.

DISCUSSION

There are several situations in the human body in which thin-walled collapsible vessels conduct blood through a cavity in which the pressure may rise considerably. Intracranial blood flow and intraocular blood flow are two examples. Because venous blood pressure in the cavity is considered to be identical to the cavity pressure, perfusion pressure is calculated as the difference between the mean arterial blood pressure and the cavity pressure. When the perfusion pressure reaches zero, the flow in the blood vessels disappears. This relationship can be applied to CBF in the bony wall of the inner ear. Cochlear perfusion pressure may be calculated as the difference between the mean arterial blood pressure and the inner ear pressure. Because endolymphatic pressure varies depending on perilymphatic pressure, both endolymphatic and perilymphatic pressures are considered as the inner ear pressure.[2] The concept of cochlear perfusion pressure is similar to that of cerebral perfusion pressure, which is calculated as the difference between the mean arterial blood pressure and CSF pressure.

Larsen[9] observed a reduction of CBF when the CSF pressure was raised to the level at which the difference between the mean arterial blood pressure and the CSF pressure fell below 5 kPa in rabbits. He observed the Cushing phenomenon, ie, a rise in mean arterial blood pressure and a decrease in pulse rate in response to elevation of CSF pressure. In the present study, upon the elevation of the inner ear pressure, the CSF pressure did not increase enough to cause the Cushing phenomenon. This finding suggests that an elevation in CSF pressure does not occur easily following the elevation of inner ear pressure. Conversely, changes in CSF pressure are transmitted completely to the inner ear pressure in guinea pigs.[10] The difference of degree of directional pressure transmission between CSF and inner ear fluid is probably because of the significant difference in volume between the cranium and the inner ear.

Increased inner ear pressure reduced CBF and impaired capillary blood flow or microcirculation more easily than arteriolar blood flow. We thought this was related to the fact that the blood pressure of the capillaries is lower than that of the arterioles. Our finding that the blood flow in the upper turns was impaired more significantly than that in the basal turn may suggest that the blood pressure is lower in the upper turns than in the basal turn in connection with the direction of blood flow of the spiral modiolar artery from the basal turn to the apex. A possibility exists that the blood pressure difference between the cochlear turns is related to the low-tone hearing loss that indicates impairment in the upper turns in Meniere's disease. In evaluating CBF by dividing the cochlea into various parts, the number of microspheres must be high in both quantitative and qualitative measurements. However, because too many microspheres may disturb the CBF, the evaluation of flow in excessively small parts is difficult from the point of view of statistical error.

Because cochlear perfusion pressure is altered by changing the inner ear pressure, relationships between cochlear perfusion pressure and CBF will be studied by use of this method in connection with a problem regarding the autoregulation of CBF. We also consider this method to be an experimental model of CBF disturbance that can be regulated at various levels. Effects of drugs or noise in the presence of impaired CBF will be studied by use of this model.

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THE DEAFNESS RESEARCH FOUNDATION
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Ann Otol Rhinol Laryngol 100:1991

ULTRASTRUCTURAL AND CYTOCHEMICAL EVIDENCE FOR SINGLE IMPULSE INITIATION ZONES IN VESTIBULAR MACULAR NERVE FIBERS OF RAT

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Cupric ion–ferricyanide labeling methods and related ferrocyanide-stained tissues were used to locate and characterize, at the ultrastructural level, presumptive impulse initiation zones in the three types of vestibular macular nerve fibers. Large-diameter, M-type vestibular nerve fibers terminate in a calyx at the heminode, and labeling is coextensive with the base of the calyx. Intermediate, M/U-type nerve fibers have short, unmyelinated preterminal segments that sometimes bifurcate intramacularly, and small-diameter, U-type nerve fibers have long, unmyelinated preterminal axons and up to three branches. Preterminals of these nerve fibers display ultrastructural heterogeneity that is correlated with labeling patterns for sodium channels and/or associated polyanionic sites. They have a nodelike ultrastructure and label heavily from near the heminode to the base of the macula. Their intramacular branches, less organized ultrastructurally, label only slightly. Results indicate that vestibular nerve fibers have one impulse initiation zone, located near the heminode, that varies in length according to nerve fiber type. Structural heterogeneity may favor impulse conduction in the central direction, and length of the impulse initiation zone could influence nerve discharge patterns.

KEY WORDS — heminodal ultrastructure, impulse initiation zone, nerve fiber heterogeneity, vestibular macula.

INTRODUCTION

Findings of recent three-dimensional reconstructions of rat macular nerve terminal and receptive fields[1,2] indicated that each calyx may be a processing element for information received from hair cells of a specific portion of the macular surface. As many as four calyces of different nerves may receive synaptic input from a given type II hair cell, but type II cells rarely communicate with more than one calyx of the same nerve. Therefore, a question arises as to whether each calyx also has its own encoding site or impulse initiation zone. The answer to this question is important in terms of information processing, since it sheds further light on other issues such as the possibility that complex interactions between branches exist, creating multiplexing phenomena and possible branch dominance.

Currently, there is no direct physiologic evidence for the site of the impulse initiation zone in vestibular nerve fibers. Electrophysiologic studies of more approachable lateral line receptors, which have hair cells but not calyces, indicate that unmyelinated preterminal axons of this system do not conduct impulses.[3-5] Action potentials appear to be initiated at the first or second node of Ranvier,[5] and neural activity prior to the node(s) is considered to be graded. However, a recent cytochemical study of fish saccular nerve fibers[6] for sodium channels provided light microscopic evidence that each branch of bifurcating, large-diameter, myelinated nerve fibers could have an impulse initiation zone. Both branches were labeled by a ferric ion–ferrocyanide method[7,8] for locating zones of increased sodium channels in axons. Saidel[6] proposed that irregularity of discharge in large-diameter nerve fibers might be due to competition between impulses initiated in the two branches. In contrast, labeling of small-diameter nerve fibers was confined to the first heminode below the neuroepithelium, strongly suggesting that these neurons have but one impulse initiation site. Regularity of discharge in small-diameter nerve fibers might then be due to continuous modulation of this single zone.

In this report, we address the question of the possible location(s) of encoding sites in the three kinds of nerve fibers identified in mammals by their myelination patterns as M-type, M/U-type, and U-type.[9] M-type nerve fibers are myelinated to a single terminal calyx; M/U type nerve fibers have short, unmyelinated, preterminal segments that sometimes bifurcate within the macular neuroepithelium; and U-type nerve fibers typically have long, unmyelinated preterminals and up to three intramacular branches. We show that unmyelinated vestibular preterminal axons are ultrastructurally heterogeneous. This heterogeneity is correlated with the labeling pattern for sodium channels and/or associated intra-axonal polyanionic sites as demonstrated by a cupric ion–ferricyanide variation of the cupric ion–ferrocyanide method of Byers and Costello.[10,11]

From the National Aeronautics and Space Administration–Ames Research Center, Moffett Field (Ross, Chee), and the San Jose State University Foundation, San Jose State University, San Jose (Black), California. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of NASA-Ames Research Center.

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Both variations depend upon cationic binding of cupric ions to sodium channels and/or associated polyanionic materials. The cupric ions subsequently combine with ferrocyanide (or ferricyanide, in this study) to form a precipitate ($Cu2Fe[CN]6$)[12] that is prominent in the axoplasm.[10,11]

Our results strongly suggest that each vestibular nerve fiber has a single zone near the heminode that on cytochemical grounds appears to be the site of impulse initiation. The length of the zone varies according to myelination pattern, so that it is long in U-type, short in M/U-type, and extremely short in M-type nerve fibers. Our findings are discussed in the context of macular information processing.

MATERIAL AND METHODS

Sprague-Dawley rats (Charles River) weighing between 215 and 350 g were used throughout. Six rats used for ultrastructural study were killed painlessly by decapitation. Their bullae were rapidly removed and fixed by immersion with the ferrocyanide method of Ernst et al,[13] which includes postfixation in 1% osmium tetroxide–1.5% ferrocyanide solution. The purpose was to enhance contrast staining of membranes and organelles.[14] The tissue was processed for transmission electron microscopy as described elsewhere.[9]

Several methods were tested for cytochemical identification of polyanionic materials and/or sodium channels. This report focuses on findings in 12 rats whose macular tissues were prepared basically by the method of Byers and Costello,[10,11] except that ferricyanide rather than ferrocyanide was used as the precipitating agent. Our variation of the method using ferricyanide gave reproducible results in four different experiments ($n = 17$). It also resulted in highly specific labeling of endoplasmic reticulum and portions of the Golgi apparatus in hair cells that was not observed with ferrocyanide.

Following decapitation, the bullae were rapidly removed and placed in fixative (2.5% glutaraldehyde buffered to pH 7.4 with 0.1 mol/L phosphate buffer), where the round and oval windows were opened and the membranous labyrinth was perfused with additional fixative. This process was completed for both inner ears within 1½ to 2 minutes. After 2 hours of immersion in fixative on a rotator, tissues were washed three times in the same phosphate buffer. Postfixation was for 1 hour in osmium tetroxide in 0.1 mol/L phosphate buffer at pH 7.4. Tissues were then washed three times in the buffer and reduced gradually from pH 7.4 to pH 6.0, whereupon the macular tissues were microdissected from the surrounding bone for incubation according to the following schedule: 1) 1.0 hour of incubation in 0.05 mol/L phosphate buffer containing 0.1 mol/L cupric sulfate and 0.068 mol/L sodium citrate, pH 6.0; 2) three washes in phosphate buffer, reduced gradually to pH 4.1; and 3) 15 minutes of incubation in 0.1 mol/L potassium ferricyanide, pH 1.9. Six maculae (three animals) were processed according to this schedule. For other groups of six maculae, the incubation times were doubled, increased to 2.5 times the minimum incubation period, or tripled. Following incubation, the tissues were washed three times in phosphate buffer (pH 4.1, pH 6, pH 7.4), dehydrated in a graded series of alcohols, and embedded in Spurr medium. Tissues were sectioned at 1.0 μm until an area of interest was found. Ultrathin (100-nm) sections were then mounted on copper grids, stained with uranyl acetate and lead citrate, and examined in a Zeiss 902 transmission electron microscope.

RESULTS

Ultrastructural Findings. The features of nodal and terminal heminodal zones of vestibular nerve fibers are illustrated in Fig 1, as a basis for discussion of reacted tissue, and only salient features are presented here.

Axons of vestibular nerve fibers decrease by about one third in diameter at the myelin sheath attachment (MySA) zone of complete nodes (Fig 1A). Myelin is consistently thicker on the central side of the node than on the peripheral side (in Fig 1A, 35 and 20 layers, respectively).

The nodal recess (Fig 1A,B), a barrel-shaped enlargement of the axon at the node, is characterized by its content of mitochondria, smooth endoplasmic reticulum (SER), and vesicles, all loosely arranged in flocculent-appearing axoplasm; and by the presence of approximately 25- to 40-nm-thick filamentous undercoating of the axolemma (Fig 1B). Neurofilaments and neurotubules are longitudinally arranged and are condensed in the central part of the nodal axon. This organization differs from that of internodal segments, in which the SER is reticular and other organelles are intermixed (Fig 1A).

The nodes are nearly completely covered by fingerlike extensions of the Schwann cell (Fig 1A,B). There is an amorphous gap substance between opposing Schwann cell processes, and other amorphous material fills the space between them and the axolemma. The gap ranges between approximately 0.025 and 0.04 μm in width in our fixed material. Basal lamina passes without interruption over the gap, from the surface of one Schwann cell to the next.

Heminodes of U-type nerve fibers (Fig 1C-E) have features in common with nodes: accumulations of vesicles occur at the periphery of the axon of the MySA zone (Fig 1E), while deeper sections show the central, compact alignment of neurofilaments and neurotubules (Fig 1C). There is a nodal recess in both unbranched (Fig 1C-E) and branched U-type nerve fibers (Fig 1E). Fingerlike extensions of one or more macular supporting cells take the place

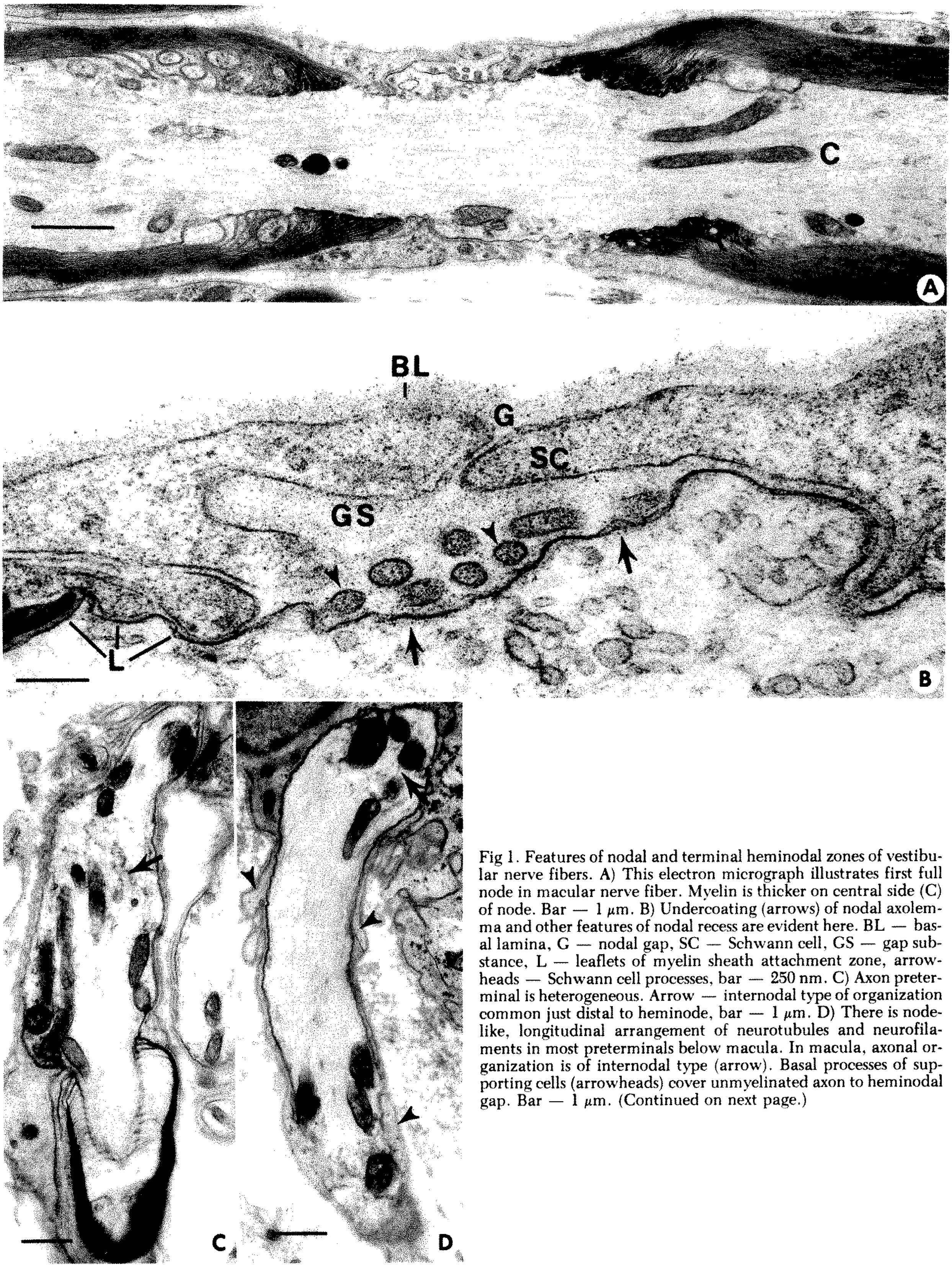

Fig 1. Features of nodal and terminal heminodal zones of vestibular nerve fibers. A) This electron micrograph illustrates first full node in macular nerve fiber. Myelin is thicker on central side (C) of node. Bar — 1 μm. B) Undercoating (arrows) of nodal axolemma and other features of nodal recess are evident here. BL — basal lamina, G — nodal gap, SC — Schwann cell, GS — gap substance, L — leaflets of myelin sheath attachment zone, arrowheads — Schwann cell processes, bar — 250 nm. C) Axon preterminal is heterogeneous. Arrow — internodal type of organization common just distal to heminode, bar — 1 μm. D) There is node-like, longitudinal arrangement of neurotubules and neurofilaments in most preterminals below macula. In macula, axonal organization is of internodal type (arrow). Basal processes of supporting cells (arrowheads) cover unmyelinated axon to heminodal gap. Bar — 1 μm. (Continued on next page.)

of the distal MySA zone (Fig 1D). Filamentous undercoating is apparent along the axolemma of the heminode, and amorphous material fills the gaps between Schwann cell and supporting cell processes. Heminodal gaps range between 0.1 and 0.5 μm in width, with gap size increasing with the length of the unmyelinated segment. The basal lamina of the Schwann cell is continuous with that of

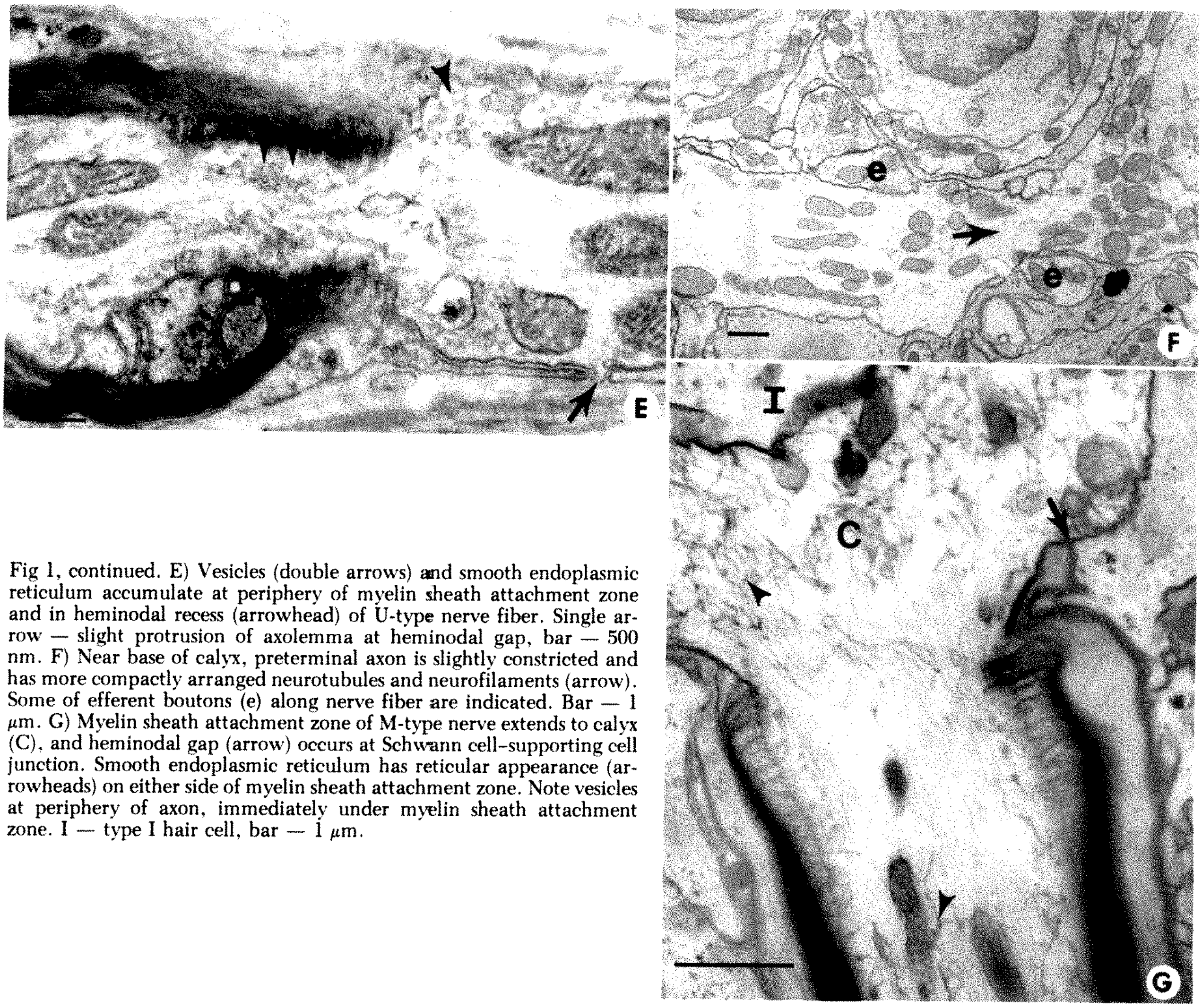

Fig 1, continued. E) Vesicles (double arrows) and smooth endoplasmic reticulum accumulate at periphery of myelin sheath attachment zone and in heminodal recess (arrowhead) of U-type nerve fiber. Single arrow — slight protrusion of axolemma at heminodal gap, bar — 500 nm. F) Near base of calyx, preterminal axon is slightly constricted and has more compactly arranged neurotubules and neurofilaments (arrow). Some of efferent boutons (e) along nerve fiber are indicated. Bar — 1 μm. G) Myelin sheath attachment zone of M-type nerve extends to calyx (C), and heminodal gap (arrow) occurs at Schwann cell-supporting cell junction. Smooth endoplasmic reticulum has reticular appearance (arrowheads) on either side of myelin sheath attachment zone. Note vesicles at periphery of axon, immediately under myelin sheath attachment zone. I — type I hair cell, bar — 1 μm.

the macula.

Axons of U-type nerve fibers are not uniformly organized distal to the recess. The preterminal axons increase in diameter by approximately 30% to 50% when compared to the diameter of the parent nerve axon. The preterminals briefly have the appearance of internodal axons (Fig 1C). They then reorganize into a more nodal configuration, which they retain until they enter the macula (Fig 1D). Patches of subaxolemmal filamentous material are present, but the undercoating does not appear to be complete. The nerve fiber is usually slightly constricted as it enters the macula. Within the neuroepithelium, the preterminal again increases in diameter and reverts to an internodal morphology (Fig 1D), which it keeps until it nears the conical base of a calyx (Fig 1F). There, neurofilaments and neurotubules briefly become more compactly arranged in the slightly constricted axon before they and other organelles disperse into the base of the calyx.

The MySA zones of both M-type and M/U-type nerve fibers lie entirely within the extracellular compartment. The basal lamina of the nerve fibers is continuous with that of the macula. A distinct nodal recess is lacking (Fig 1G), its place being occupied by the base of the calyx, and undercoating is not evident. In M-type nerve fibers, the heminodal gap is small (about 0.02 μm) and lies between a Schwann cell and a macular supporting cell at the base of a calyx. The reticular organization of SER is evident proximal to the MySA zone and in the base of the calyx. In the MySA zone, vesicles and SER are largely segregated to the periphery of the axon.

Cupric Ion-Ferricyanide Reacted Material. Figure 2A illustrates the moderate amount of reaction product typically present at nodes of Ranvier ($n = 16$) of macular nerve fibers in tissue in which incubation periods were increased by factors of 2.5 or 3. Both paranodal and MySA zones show reaction product, but large particles are most concentrated in the recess and in the axoplasm of the nodal zone. Dustlike particles are present along the axolemmal undercoating, but in general, all membranes of these maculae are more poorly stained than are those in comparable tissue prepared with ferrocy-

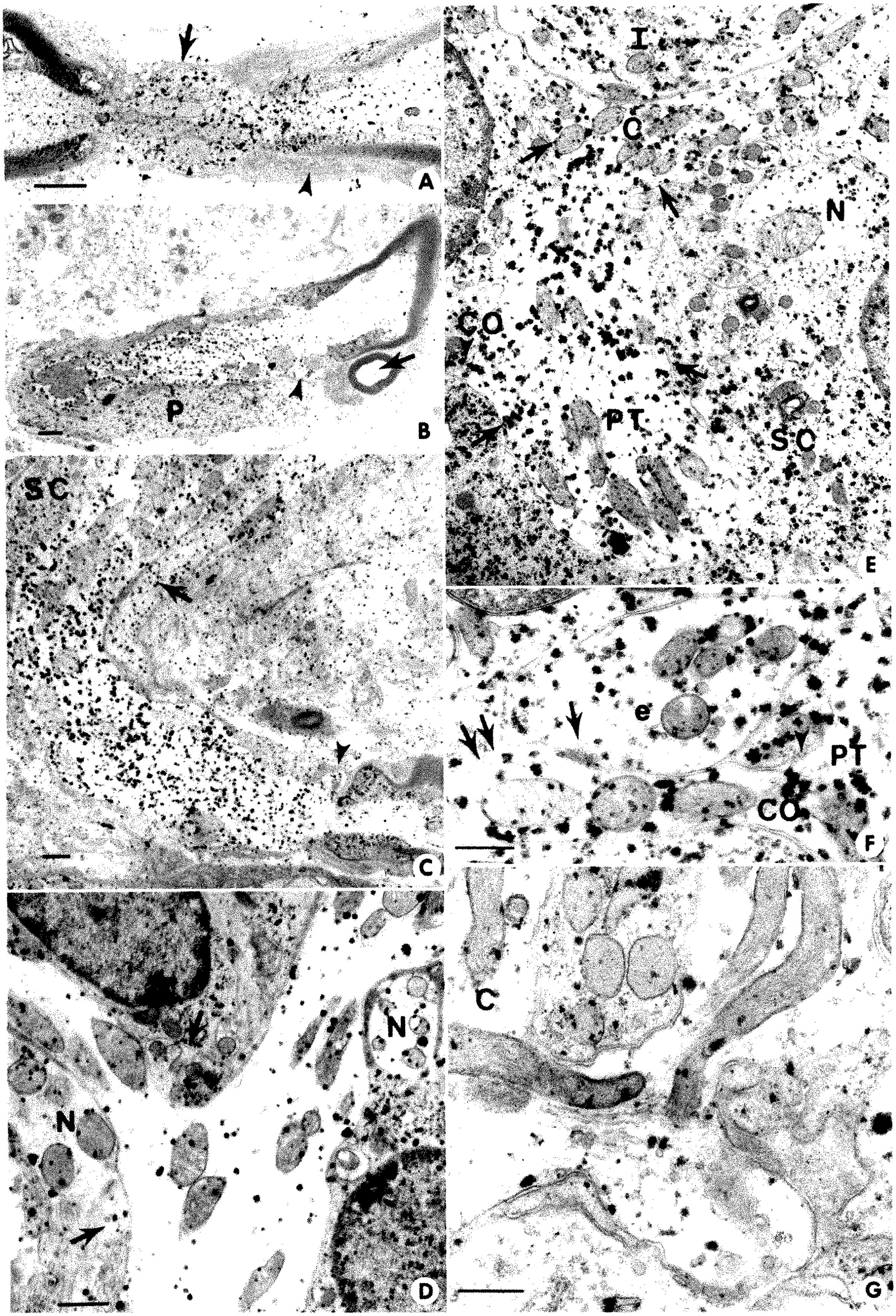

Fig 2. Cupric ion–ferricyanide reacted material. A) Nodes of macular nerve fibers label moderately (arrow). Myelin sheath attachment zone is lightly labeled. Scattered particles occur along basal lamina but are absent from Schwann cell cytoplasm (arrowhead). B) Macular preterminals of U-type nerve fibers typically show greatest labeling distal to heminodal recess (arrowhead). Supporting cell process (P) around unmyelinated axon is slightly labeled, and there are scattered particles in neighboring connective tissue. (Continued on next page.)

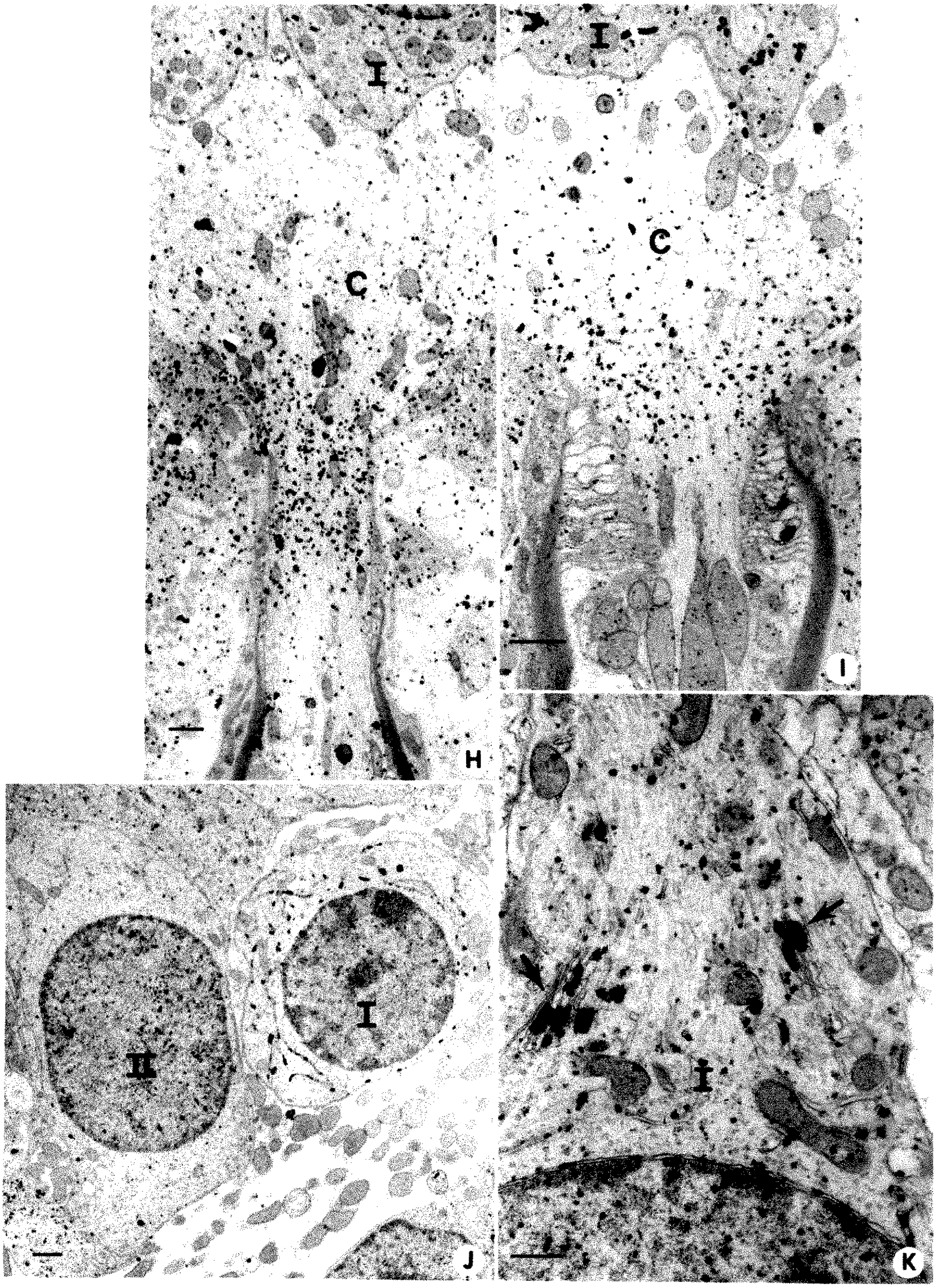

Fig 2, continued. Arrow — adjacent nerve fiber that is proximal to its heminode and lacks staining. C) Zonal staining of U-type preterminals below macula. Arrowhead — nodal recess. Particles are larger and more numerous distal to heminodal zone, up to site of penetration of macula (supporting cell [SC]). Smaller preterminal axon (arrow) has fewer and smaller particles. D) Intramacular nerve fibers typically show slight labeling not increased at bifurcations. Right branch is approaching calyx, not in view, at upper right and shows slightly more deposits. Arrows — efferent boutons on axon, near and at bifurcation, N — neighboring nerve fibers. E) This unmyelinated preterminal (PT) shows much labeling near calyx (zone between arrows). More proximal part of axon is less heavily labeled. Collateral (CO) sprang from PT (arrowhead) and is illustrated in F. I — type I hair cell, C — calyx. F) Vesiculated, efferent-type collaterals are stained. This collateral (CO) originated from preterminal (PT) shown in E (arrowhead). Double arrows help define its membrane. Efferent bouton (e) synapses (single arrow) with CO. Many vesicles contain reaction product, and there is labeling of synaptic site. G) Mixed-type calyceal collaterals show few deposits. H) Labeling in M/U-type nerve fibers. I — type I hair cell. I) Labeling in M-type nerve fibers. J) Cells from macula. Reaction product is present in perinuclear compartment and in endoplasmic reticulum. Type II hair cell (II) shows little or no labeling. K) Cells from macula. Reaction product is present in some Golgi cisterns (arrows) of type I cell (I). Bars in A-C, H-J — 1 μm; in D,F,G,K — 500 nm.

anide. Small particles fill the myelin leaflets of the MySA zone, but the Schwann cell is free of reaction product. A few particles are associated with the basal lamina. Gap substance is diminished and the remaining fragments are not labeled.

Figure 2B illustrates the comparable reaction product observed at heminodes. The paranodal zone and the portion of the axon covered by the myelinating Schwann cell are lightly stained, while axoplasm distal to the nodal gap is more heavily labeled. Schwann cell nuclei and cytoplasm are free of reaction product, and axons proximal to paranodes show little or no staining. Particles are present in supporting cell processes enclosing unmyelinated segments below the neuroepithelium and are scattered along filaments of the subneuroepithelial connective tissue.

Figure 2C illustrates a heavily labeled, large preterminal of a U-type nerve and the rather uniform, moderate staining of an adjacent, smaller unmyelinated nerve fiber. Staining is light in the nodal recess and at the heminode of the larger nerve, but it gradually increases in amount more distally. A zone of heavy deposits extends to a level just beyond penetration of the macula.

Preterminal axons with long courses through the macula have scattered particles of deposit (Fig 2D). Particles are not increased numerically at branch points in those few (n = 4) examples in which both branches were clearly observed, but they do increase slightly in number as the axon approaches a calyceal terminal (Fig 2D). Efferent boutons synapsing on the axons and at bifurcations also label, with some deposits in their vesicles. Tissues in which the incubation periods were tripled have heavier deposits in the intramacular segments of preterminals, particularly near the calyx. In one case, included here for completeness, an unmyelinated preterminal showed heavy deposits near a calyx (Fig 2E); a neighboring preterminal was more moderately labeled (Fig 2E). The heavily labeled preterminal gave off an efferent-type, vesiculated collateral (arrowhead, Fig 2E; better shown in an adjacent section [Fig 2F]) that also was stained. In general, small-diameter, efferent-type collaterals are labeled, and both they and efferent boutons have particles deposited within some of their vesicles (Fig 2F). Calyceal collaterals that have both afferent (larger-diameter, electron-lucent) and efferent (beaded, vesiculated) properties show less reaction product (Fig 2G).

Figure 2H,I illustrates labeling in M/U-type and M-type nerve fibers in tissue in which the incubation periods were increased by a factor of 2.5. In both cases there are deposits in a discrete zone beginning at the level of the last few myelin leaflets of the MySA zone and ending in the base of the calyx. This zone is very short in M-type nerve fibers. The calyces contain scattered particles.

Another finding is that type I hair cells have reaction product in portions of the endoplasmic reticulum that extend from the nuclear envelope through the Nissl substance to hypolemmal cisterns along the cell membrane, and in some of the Golgi cisterns. Some of these deposits are illustrated in Fig 2J,K. There are scattered particles in nuclei of both type I and type II hair cells, but type II hair cells typically show little staining of endoplasmic reticulum (Fig 2J).

DISCUSSION

Our ultrastructural results show that peripheral, preterminal axons of U-type macular nerve fibers are heterogeneous both in size and in subcellular organization. Such heterogeneity is lacking in short preterminal axons of M/U-type nerve fibers, and M-type nerve fibers lack preterminal segments altogether. These differences in organization are related to the geometry of the nerve endings and to the sites and length of the putative impulse initiation zone as revealed by the stain used. Because the calyx is located at the heminode in M-type nerve fibers and gives origin to vesiculated, efferent-type collaterals that terminate on type II hair cells, we consider calyces to be highly specialized axon segments. Previously, Spoendlin[15] referred to the calyx as an axon.

Preterminal heterogeneity in axons of U-type nerve fibers should be considered together with the finding that myelination and therefore nerve fiber diameter increases in the central direction at the first node and again on the central side of the cell body.[16] Additionally, efferent boutons are strategically located to influence information processing in the central direction: they are prominent on calyces, on unmyelinated branches, and at bifurcation sites, but are rarely found more proximally along preterminals.[1] The constellation of morphologic features noted could underlie functional polarization of axons subserving a sensory function to favor transfer of information in the central direction. Additionally, differences in peripheral geometries at the sensory end of the axons should influence nerve discharge patterns, just as geometric properties influence output of conducting and distributing portions of axons, for which more experimental and modeling data are available.[17,18]

Ultrastructural heterogeneity in peripheral axons of vestibular nerve fibers is congruent with their labeling patterns. The zonal labeling pattern in heminodes of preterminals of U-type nerve fibers appears to be comparable to that reported previously for Ruffini-like endings.[10]

In rat vestibular nerve fibers, axon segments immediately distal to the zone covered by the Schwann cell are consistently labeled. This strongly suggests that in all three kinds of nerve fibers the impulse initiation zone is located in these segments. This interpretation is in basic agreement with the previous results of Saidel[6] in fish saccular maculae, but his observation of multiple encoding sites in arborizations of large-diameter myelinated axons was not corroborated. In the rat macula, large-diameter myelinated axons are M-type nerve fibers that end in single calyces, do not branch, and have single, very short zones at the base of the calyx that label for sodium channels. Such units, called "calyceal units" by Goldberg et al,[19] always had irregular discharge patterns. Therefore, Saidel's hypothesis that regularity or irregularity in discharge may be determined by the number of encoding sites is not valid across species.

In rat maculae, the length of the segment interpreted here to be the impulse initiation zone is related to the distance from the heminode to penetration of the fibers into the macula (Figs 1C and 2H,I). This distance is in turn related to other properties of the nerve fiber, such as its myelination pattern and peripheral geometry. Thus, it is likely that the length of the impulse initiation zone is one of a number of features that collectively determine nerve discharge rate and pattern.

Our present ultrastructural and cytochemical findings suggest that other zones in preterminal axons of vestibular nerve fibers, particularly the precalyceal, may have slightly increased numbers of sodium channels and/or associated polyanionic substances that may prove to be important to information processing. But these zones do not correspond to an encoding site in which nerve impulses originate. The site of impulse initiation is near the heminode, according to previous findings in fish[6] and the present observations in rat macular nerve fibers.

The atypical finding of heavy labeling near the calyx in an unmyelinated nerve fiber (Fig 1E) will require further investigation. This labeling occurred near the origin of an efferent-type collateral, which typically stain. Whether the increased deposits in this preterminal are related to the presence of the collateral is unknown. The simplest explanation is that the labeling may have resulted from diffusion and thus may be artifactual. Alternatively, while variations in labeling could be due to sometimes poor penetration of the reacting solutions into the macula, they might reflect true differences in numbers of ion channels or differing levels of activity of the nerve fibers in the living state. It has been demonstrated[20] that nodes of nerve fibers electrically excited at high frequencies show more cation binding.

Labeling of endoplasmic reticulum and of the nuclear envelope in type I hair cells occurred in every tissue in which the incubation period was increased by a factor of 2 or more, even though the total amount of staining differed from cell to cell. The nature of the labeled material in type I hair cells is completely unknown, and ascertaining its properties is beyond the scope of this research. Such labeling has not been reported previously in other tissue prepared by the ferrocyanide method[9,10] and did not occur in our own tests in which ferrocyanide was employed. It is not clear why greater reproducibility in results occurred from experiment to experiment when ferricyanide was substituted for ferrocyanide, or why staining of additional intracellular organelles was observed. Several alternative explanations are possible, the simplest being that vestibular hair cells are unique in these regards. Another is that our method may have provided more radicals to promote the chemical reaction. Further, it is possible that the ferro form of the cyanide absorbs more strongly to membranes than does ferricyanide, reducing the amount that penetrates axons to react with the cupric ions. Ferricyanide, which is more mobile because it is less strongly absorbed, is able to penetrate the tissue better and more deeply, to enhance formation of reaction product. A greater tendency for the ferro form to be absorbed at membranes could also explain the more dense reaction product subjacent to nodal membranes in tissue prepared by the ferric ion–ferrocyanide method.[7,8] Our results, in which staining of membranes was reduced in tissue exposed first to cupric ions and then reacted with ferricyanide, would support this hypothesis.

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The Voice Foundation will sponsor a state-of-the-art conference on Spastic Dysphonia, to be held July 20, 1991, at the Warwick Hotel in Philadelphia, Pennsylvania. For further information, contact The Voice Foundation, 1721 Pine Street, Philadelphia, PA 19103; (215) 735-7999.

Ann Otol Rhinol Laryngol 100:1991

DISTRIBUTION OF MAST CELLS IN THE TUBOTYMPANUM OF GUINEA PIGS

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The distribution pattern of mast cells in the middle ear mucosa and eustachian tube was examined histologically in adult and developing guinea pigs. The aim was to better understand the role of mast cells in the middle ear defense mechanism. The density of mast cells was highest in the pharyngeal orifice of the eustachian tube, and decreased in the direction of the tympanic orifice. The density was higher in adults than in developing animals. Mast cells were also found in the tubotympanic membrane of the fetal guinea pig. Mast cells in the middle ear mucosa appeared in areas covered by ciliated epithelia or areas richly vascularized. Almost all mast cells found in the middle ear and eustachian tube mucosa were the connective tissue type. The results of this investigation suggest that mast cells distribute in the tubotympanum in response to continuous stimuli to the tubotympanic cavity.

KEY WORDS — eustachian tube, guinea pig, mast cell, middle ear.

INTRODUCTION

The middle ear is an organ capable of responding immunologically to antigenic substances. There are few immunocompetent cells (lymphocyte, macrophage, etc) in the normal middle ear mucosa.[1,2] However, Lim et al[3,4] reported that mast cells are often found in the lamina propria of the human and guinea pig middle ear mucosae. Hentzer[5] also demonstrated mast cells in the subepithelial connective tissue of the human middle ear mucosa. Alm et al[6] and Widemar et al[7] reported that the pars flaccida of the tympanic membrane of humans and rats accommodates numerous mast cells. Mast cells have been clarified to be a factor in type 1 and type 3 allergic inflammatory reactions. As seen in these studies, mast cells with biologically active compounds are considered to be involved in the pathogenesis of middle ear disorders such as production of fluid in otitis media with effusion. However, there were no detailed investigations in the literature of the distribution of mast cells in the tubotympanic membrane. Therefore, the distribution of the mast cells in the tubotympanic membrane of the guinea pig was investigated. In the present study, an image processor (Nexus 6800) was used in order to analyze mast cells quantitatively. In addition, changes in the distribution with aging were investigated.

MATERIALS AND METHODS

Animals. Ten Hartley strain healthy male guinea pigs (body weight, 300 to 400 g) — nine from 8 to 10 weeks' fetal age, nine 1 day's postnatal age, and nine 2 weeks' postnatal age — were used. All animals, bred in conventional conditions, were supplied from a local breeder and maintained in the animal facility at the Medical College of Oita (Japan). They were confirmed to be free of middle ear infection.

Tissue Processing. Tissue processing was carried out as follows. Guinea pigs were anesthetized by an intraperitoneal injection of pentobarbital sodium solution, underwent heart puncture, and were decapitated painlessly. The skulls of the guinea pigs were bisected at the midline and cut by an EXAKT cutting grinding system (EXAKT, Hamburg, Germany). For light microscopy, the skulls containing bullae and eustachian tubes were fixed with Karnovsky's fixative solution (0.2 mol/L cacodylate buffer containing glutaraldehyde at 2.5% and formaldehyde at 2.0%) and Bouin's solution. The specimens were decalcified by the method of Plank and Rychlo[8] or 10% ethylenediaminetetraacetic acid in 0.1 mol/L Tris buffer (pH 6.95). After decalcification, the specimens were dehydrated with graded ethanol and embedded in paraffin or glycol methacrylate (JB-4, Polysciences, Warrington, Pa). Sections, 8 or 4 μm, were made and stained with hematoxylin and eosin for general observation, with periodic acid–Schiff to demonstrate mucosubstances of the secretory cells, and with toluidine blue (pH 7) to demonstrate the mast cells. For scanning electron microscopy, three adult and three fetal ears were fixed with Karnovsky's fixative solution to observe the distribution of the ciliated cells. After fixation, the specimens were postfixed in buffered 2% osmium tetroxide for 2 hours, dehydrated through graded concentrations of ethanol, and dried by the critical point method. The specimens were then coated with gold and examined with a scanning electron microscope (JSM-25A; JEOL, Tokyo, Japan).

Quantitative Analysis of Mast Cells. To quanti-

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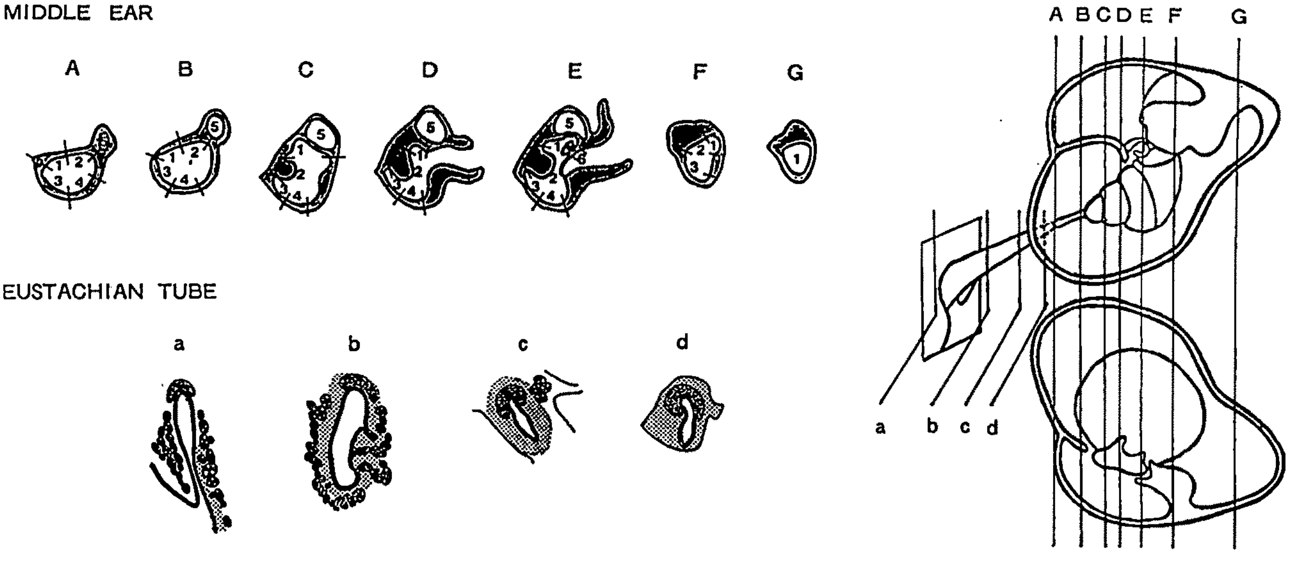

Fig 1. Schematic drawings of left tympanic bulla and eustachian tube of guinea pig. A through G and a through d are cross-sectional views of tympanic bulla and eustachian tube at levels marked in schema at right. In middle ear, each section was divided into one to five portions. In eustachian tube, number of mast cells was counted in dotted area.

tate mast cells at the lining epithelium of the tubotympanum, the number of mast cells was counted in a given length of the section. Sections for quantitative study were decalcified by the method of Plank and Rychlo,[8] embedded in paraffin, and sliced 8 μm thick. As seen in Fig 1, the middle ear mucosa was divided into 30 portions, and the eustachian tube into 4 portions. Cahn and Nutting[9] reported that the number of particles per unit volume is related to quantities obtained in the examination of micrographic specimens. Also, the number of particles per unit surface area cannot be exactly calculated if the overlapping of the particles is neglected. When we observe a section of thickness (t) taken from a random distribution of spherical particles of diameter (d) in a matrix, the particles sectioned by the upper and lower boundary surfaces of the matrix are considered together with the particles lying completely between the boundary surfaces. For this reason, there is an overlapping of the particles when the thickness of the section is regarded as t. Therefore, in order to avoid this overlapping, the thickness of the section was revised to $d/2 + t + d/2$ in our study. The thickness of the section and the diameter of a mast cell were regarded as 8 μm and 12 μm, respectively, the length of the mucosal surface was measured by a Nexus 6800 image processor (Kashiwagi Research Co, Tokyo, Japan), and the surface area of the mucosa was calculated from the revised thickness.

Statistical Analysis. Statistical analysis was performed with Student's *t* test.

RESULTS

Distribution of Mast Cells in Tubotympanic Membrane. The results in adult guinea pigs are shown in Figs 2 and 3. In adult middle ear mucosa, most of the mast cells were located in the lamina propria and underneath the epithelial layer. Few mast cells were located in the epithelial layer (Fig 4A). The density of the mast cells was highest in the superior portion of the tympanic orifice of the eustachian tube, and next highest in the pars flaccida. The density was comparatively high at the lateral site of the hypotympanum, especially near the inferior part of the bony annulus surrounding the pars tensa. Few mast cells were seen in the mucosa of the dorsal bulla, around the ossicular chain, over the promontory, or in the mucosa of the pars tensa. The mast cells in the middle ear mucosa appeared in areas covered by ciliated epithelia or areas richly vascularized. In the eustachian tube, as in the middle ear, most of the mast cells were located in the lamina propria and underneath the epithelial layer. However, a small number of mast cells were also located in the epithelial layer near the pharyngeal orifice.

The results in developing guinea pigs are shown in Figs 2 and 3. In fetal guinea pigs, mast cells were widely scattered in the middle ear mucosa (Fig 5). A few mast cells were seen in the mucosa of the dorsal bulla and over the promontory, although the number was much less than in adults (Fig 4B). In fetal eustachian tubes, the density of mast cells was lower than in adults. In the fetal pharyngeal orifices of eustachian tubes, the number of mast cells located in the epithelial layer was smaller than in adults. The density of mast cells increased with age in the eustachian tube (including the pharyngeal orifice and tympanic orifice), the superior portion of the tympanic orifice, the pars flaccida, and the bony annulus surrounding the pars tensa. On the other hand, the density of mast cells decreased in the dorsal bulla and over the promontory. In the other portion of the middle ear, the density of the mast cells showed no change with age.

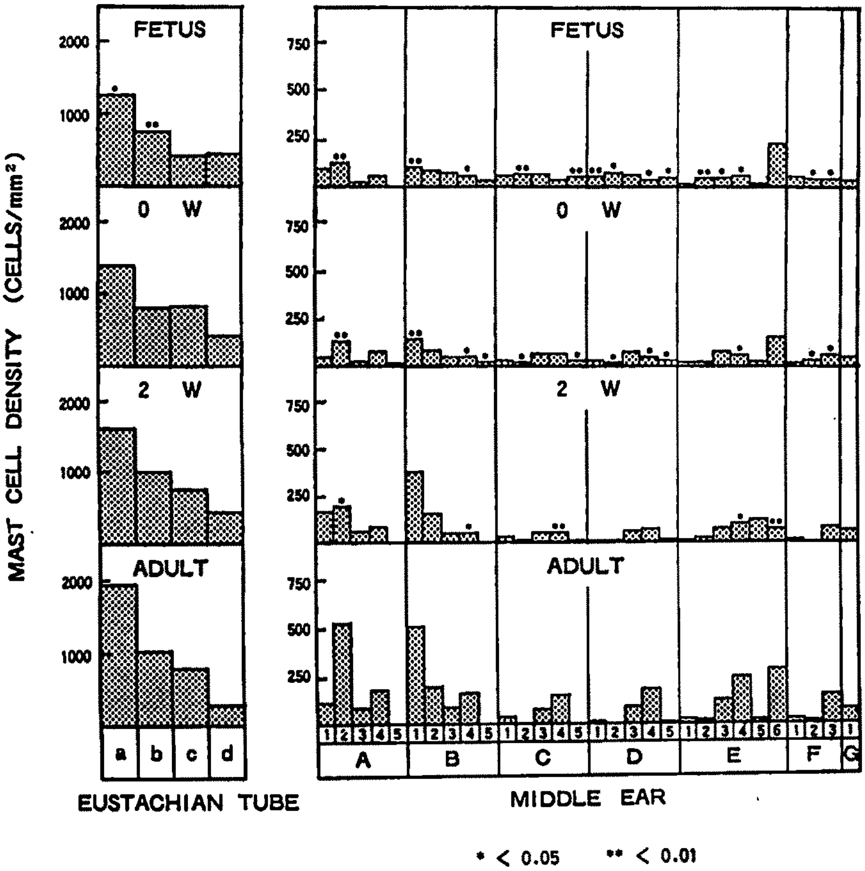

Fig 2. Density of mast cells in tubotympanum of adult and developing guinea pigs. Letters a through d show portions of eustachian tube, and A through G those of tympanic bulla, as indicated in Fig 1. Asterisks — significant differences, as compared to adults, W — weeks.

Distribution of Ciliated Cells in Tubotympanic Membrane. Figure 6 shows the distribution of ciliated cells in the tubotympanic membrane of guinea pigs. The distribution of ciliated epithelia in fetal guinea pigs was not different from that in adults. However, the secretory cells were more numerous in adults than in fetuses, as seen in the sections stained with periodic acid-Schiff reagent.

DISCUSSION

The results of this study demonstrate that the density of mast cells in the tubotympanic membrane of adult guinea pigs is highest in the pharyngeal orifice of the eustachian tube, decreasing toward the tympanic cavity. In the tympanic cavity, the density of mast cells was high in the superior portion of the tympanic orifice of the eustachian tube, pars flaccida, and bony annulus surrounding the pars tensa, in that order. Mast cells were mainly located in areas covered by ciliated and secretory epithelia, and most of them were seen in the subepithelial layer of the mucosa.

Albiin et al[10] previously investigated the distribution of mast cells in the rat middle ear. According to their study, mast cells were reported to be most numerous in the pars flaccida and anterior part of the floor of the tympanic bulla. Of interest, they reported that mast cells appear within areas covered by ciliated and secretory cells or richly vascu-

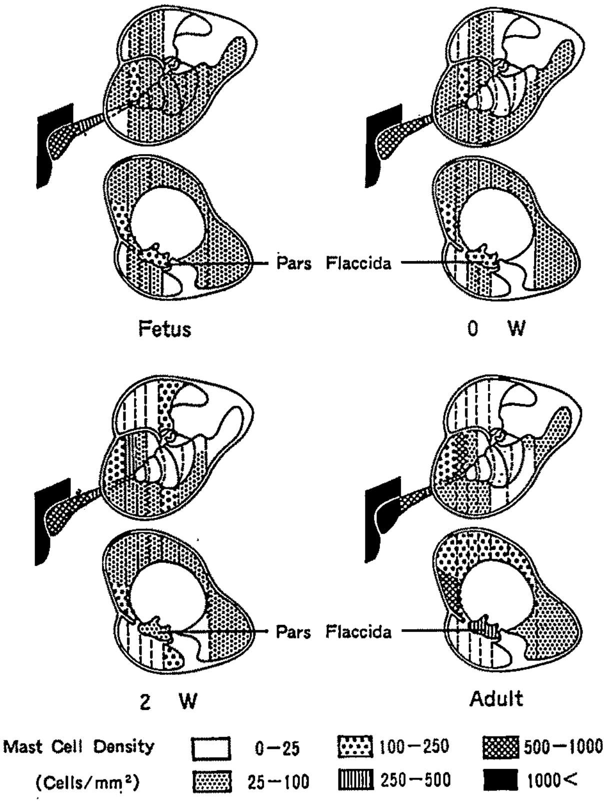

Fig 3. Graphic view of distribution of mast cells in tubotympanum of adult and developing guinea pigs. W — weeks.

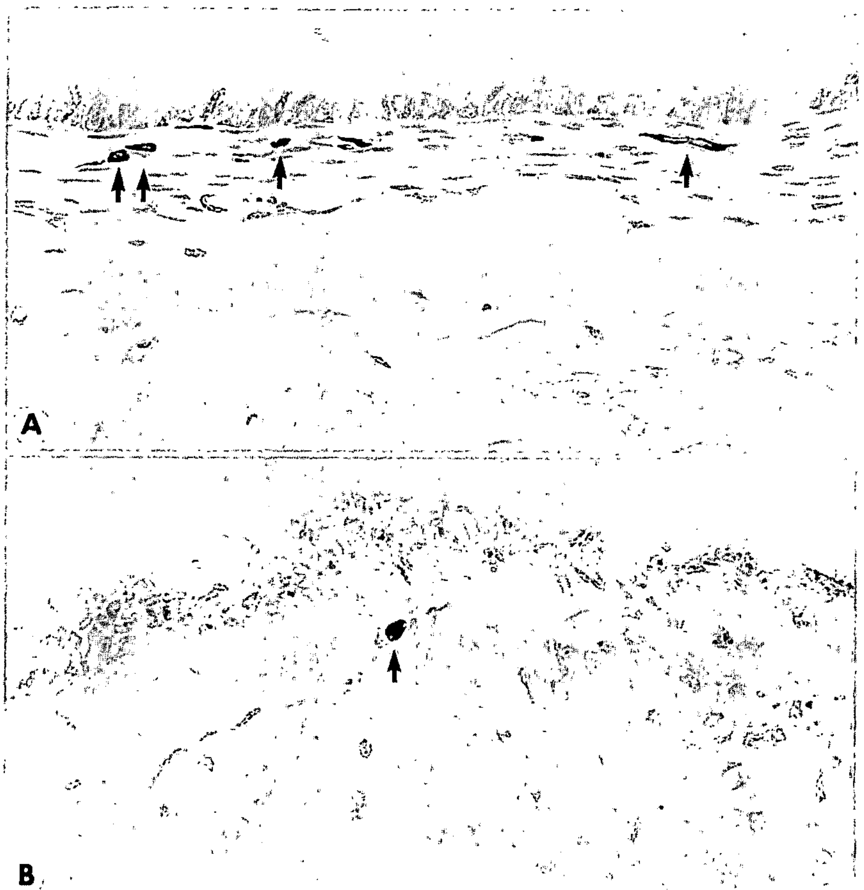

Fig 4. Histologic sections of tympanic cavity near tubal orifice (original x80). Arrows — mast cells. A) Adult. B) Fetus.

larized. Our results with guinea pigs demonstrated that mast cells were most numerous in the superior part of the tympanic orifice of the eustachian tube. This difference in the distribution pattern of mast cells in the middle ear between guinea pigs and rats might be due to the difference in species. Our results show that mast cells are observed not only in the pars flaccida, but also in the superior portion of the tympanic orifice.

We also investigated the mucosa of the eustachian tube. The density of mast cells was higher in the eustachian tube than in the middle ear, increasing toward the pharyngeal orifice. The mucosa of the eustachian tube was covered by a ciliated and secretory epithelium. Most of the mast cells were seen in the subepithelial layer of the mucosa. However, in the pharyngeal orifice of the eustachian tube, a small number of mast cells were also seen in the epithelial layer of the mucosa. Furthermore, we investigated the distribution of mast cells in the tubotympanum of developing guinea pigs. The density of mast cells in fetal guinea pig tubotympanums was significantly lower than that in adults. The number of secretory cells was more numerous in adults than in fetuses.

Throughout the middle ear and eustachian tube, mast cell distribution was in accordance with the distribution of the ciliated and secretory epithelium. Several experimental studies have indicated that flat epithelial cells in middle ear mucosa can be changed to either ciliated or secretory cells by pathologic stimuli.[11-15] On the other hand, Jeffery[16] suggested that the appearance of mast cells in the airway epithelium is indicative of disease and is not a normal feature. In conjunction with these previous reports, the results of the present study suggest that mast cells appear in the tubotympanic membrane in response to continuous stimuli (chemical, physical, and biologic).

It has been suggested that mast cells play an important role in the pathogenesis of otitis media with effusion. Recently, high levels of histamine were found in human middle ear effusions and in those of experimental otitis media with effusion. It has been suggested that histamine in middle ear effusions is derived from mast cells located in the middle ear mucosa.[6;17-19] Mogi and Bernstein[20] suggested that immune complexes and other substances in the middle ear effusion may activate complement components, leading to the production of inflammation-generating fragments. These may activate mast cells to release inflammatory mediators producing vasodilatation and mucosal edema, as well as neutrophil chemotaxis.

The exact role of mast cells in normal ear mucosa is yet unknown. Recent in vivo and in vitro studies have shown that mast cells are progeny of the multipotential hematopoietic stem cell. Mast cell pre-

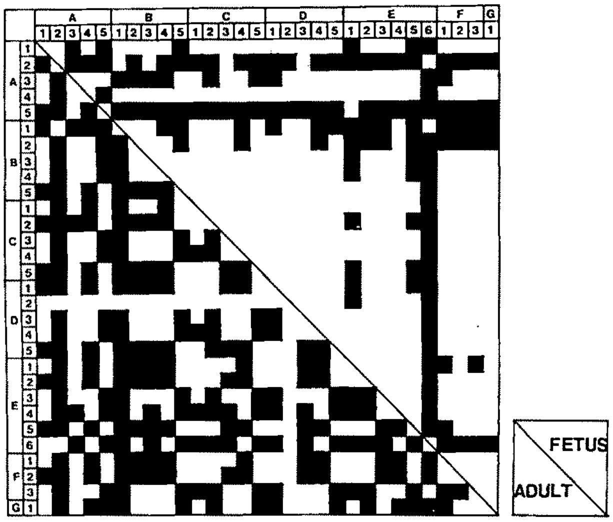

Fig 5. Difference in mast cell density among middle ear portions. A through G and arabic numbers show portions of middle ear as indicated in Fig 1. Closed squares — significant difference (p<.05).

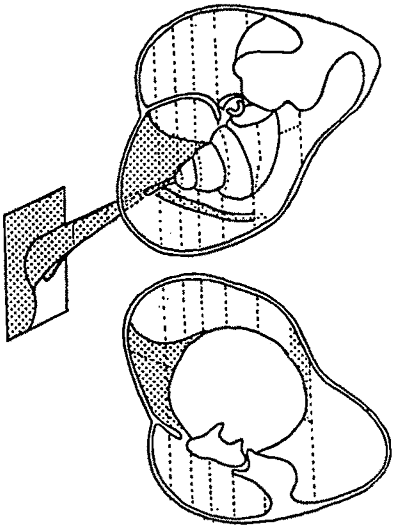

Fig 6. Distribution of ciliated cells in tubotympanum of both adult and fetal guinea pigs. Dotted areas — ciliated cells as indicated by scanning electron microscopy.

cursors (which are progeny of multipotential hematopoietic stem cells) leave hematopoietic tissues, migrate in the bloodstream, enter connective tissues, and finally proliferate and differentiate into mast cells.[21] One of the major mediators responsible for mast cell growth is interleukin 3.[22] This lymphokine is derived from many different cells such as T cells, keratinocytes, myeloid cells, and epidermal cells. Judging by the distribution pattern of mast cells in the tubotympanums of adult and developing guinea pigs, mast cell precursors may infiltrate tubotympanal mucosa and differentiate into mast cells locally as a result of immunologic events caused by antigenic stimulation during development, and may be involved in the local defense system in the tubotympanum. It was reported that biologically active compounds of mast cells induce changes in blood flow and permeability causing the flooding of plasma and leukocytes that facilitate the removal of antigenic substances.[23]

However, in our study, even though the number was small, mast cells were located in fetal tubotympanums that had received no antigenic stimuli. Biologically active compounds of mast cells have the ability to act on a wide range of target cells. Mast cell functions to be considered include immediate hypersensitivity and other inflammatory reactions, including angiogenesis, fibrosis, and tissue repair.[22] Considering the diversity of mast cell functions, there is a possibility that mast cells play another, as yet unknown role in the tubotympanum. Further examination of the function of mast cells in the tubotympanum, including in vitro study, is necessary.

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Ann Otol Rhinol Laryngol 100:1991

ENDOSCOPIC LASER THERAPY FOR OBSTRUCTING TRACHEOBRONCHIAL LESIONS

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The Lahey Clinic experience using laser bronchoscopy for relief of obstructive tracheobronchial lesions during a 7-year period from 1982 to 1989 involves 269 patients treated with 400 procedures. The carbon dioxide (CO2) laser was used for tracheal stenosis and granulation tissue. The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser was used for all obstructing endobronchial neoplasms. Indications for therapy included severe dyspnea, hemoptysis, and postobstructive pneumonitis. All patients had relatively central lesions. A rigid bronchoscope was used to treat 88% of patients, and 12% of patients were treated with a flexible bronchoscope. One death occurred during the intraoperative period. Eleven deaths occurred within 1 week of therapy and were related to the presence of extensive malignant lesions or to coronary artery disease. Our experience indicates that bronchoscopic application of the CO2 or Nd:YAG laser affords effective palliation for patients with obstructive tracheobronchial lesions. The Nd:YAG laser is recommended for patients with bulky vascular endobronchial neoplasms, and the CO2 laser is best reserved for patients with benign tracheal stenosis and granulation tissue.

KEY WORDS — bronchoscopy, endobronchial neoplasms, endoscopic laser therapy, granulation tissue, laser, stenosis, trachea.

INTRODUCTION

The application of laser technology to the endoscopic treatment of patients with tracheobronchial disorders began in 1973 with the use of the carbon dioxide (CO2) laser to ablate benign tumors.[1] Since then, several types of lasers have proved to be precise, powerful, and relatively safe tools for endoscopic management of lesions obstructing the airway.[2,3] The effectiveness and safety of laser application in bronchology were enhanced after the introduction of the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.[3-6] The special hemostatic qualities of this laser's energy make it the most suitable laser for endoscopic removal of malignant tracheobronchial lesions. At the Lahey Clinic Medical Center, we have employed laser bronchoscopy for more than 7 years. Our experience with 400 procedures performed on 269 patients between August 1982 and August 1989 is reviewed.

PATIENTS, MATERIALS, AND METHODS

At our institution, patients were referred for bronchoscopic laser therapy because of severe or rapidly deteriorating dyspnea, persistent hemoptysis, uncontrolled cough, or postobstructive pneumonia caused by malignant or benign intraluminal lesions obstructing the trachea, bronchi, or both. All patients underwent diagnostic fiberoptic bronchoscopy, which was performed either by the referring physician or by a member of our laser team. An attempt was made to exclude patients with obstruction that was primarily caused by compression by an external tumor or by submucosal malignant infiltration. All patients had a complete history taken and underwent physical examination. Preoperative workup has been described previously.[7,8]

The majority of patients were treated in an operating room under general intravenous anesthesia (thiopental sodium) and manual Venturi jet ventilation (Fig 1). Some patients were treated after receiving topical anesthesia (lidocaine hydrochloride) and intravenous sedation (diazepam, midazolam hydrochloride [Versed], and fentanyl citrate). Other patients were treated in the bronchoscopy suite and received topical anesthesia (lidocaine hydrochloride) and intravenous sedation (midazolam hydrochloride).

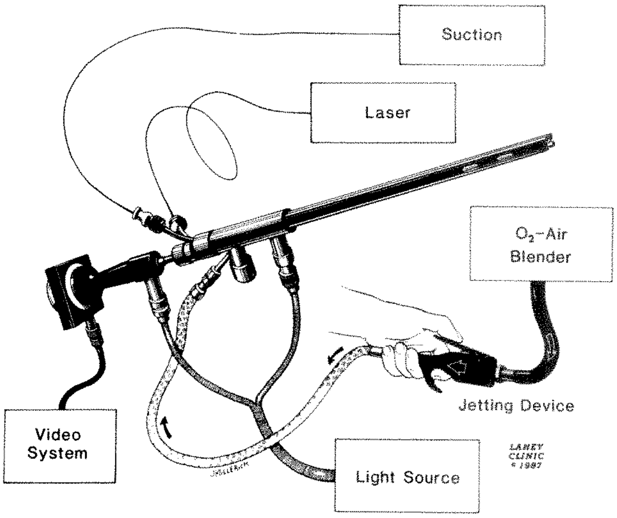

Fig 1. Rigid bronchoscope system for neodymium:yttrium-aluminum-garnet laser bronchoscopy. (By permission of Lahey Clinic.)

From the Section of Pulmonary Medicine (Beamis, Vergos), the Department of Otolaryngology–Head and Neck Surgery (Rebeiz, Shapshay), and the Eleanor Naylor Dana Laser Research Laboratory (all authors), Lahey Clinic Medical Center, Burlington, Massachusetts.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.

REPRINTS — John F. Beamis, Jr, MD, Section of Pulmonary Medicine, Lahey Clinic Medical Center, 41 Mall Rd, Burlington, MA 01805.

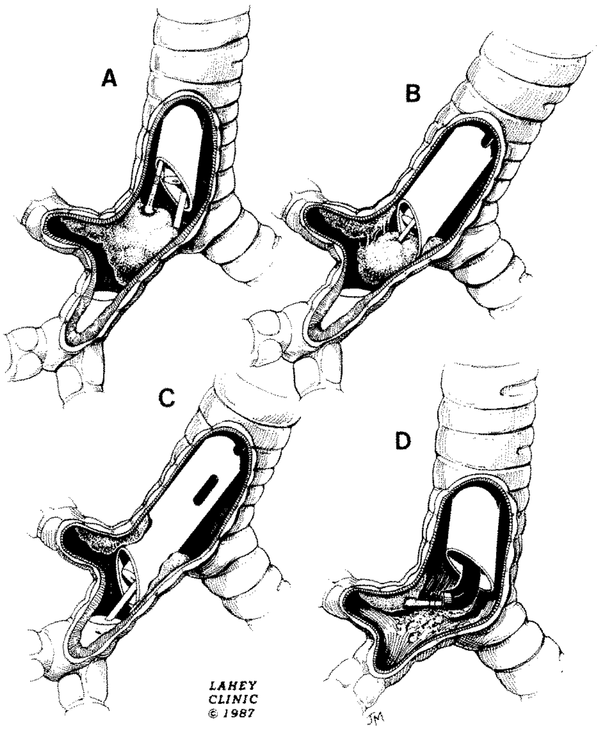

Fig 2. Technique of neodymium:yttrium-aluminum-garnet laser bronchoscopy. A) Photocoagulation of lesion. B) Lesion resected with tip of bronchoscope and delivered into barrel of scope. C) Distal airway is suctioned clear of secretions. D) Laser beam is passed through flexible bronchoscope within rigid bronchoscope to treat tumor bed. (By permission of Lahey Clinic.)

A ventilating rigid bronchoscope (Karl Storz Endoscopy-America, Inc, Culver City, Calif) was used in the majority of patients. The Hopkins 0° telescope was used in all patients examined with the rigid bronchoscope. In some patients, both rigid and flexible fiberoptic bronchoscopes were used. In the bronchoscopy suite, laser therapy was performed solely with flexible bronchoscopy.

Patients who received general anesthesia were ventilated through the Storz bronchoscope with a manual jet ventilation system developed at the Lahey Clinic (Fig 1). A 100-W Nd:YAG laser system (Cilas, Compagnie Industrielle des Lasers, Marcoussi, France, or LaserSonics Model 8900, Heraeus LaserSonics, Santa Clara, Calif) was used. The laser energy was delivered through a coaxial quartz fiber 2.4 mm in diameter. The laser power delivered ranged between 20 and 40 W. The laser pulse duration varied between 0.7 and 1.0 seconds.

Patients with benign stenosis were treated in the operating room with a 50-W CO_2 surgical laser (Heraeus LaserSonics). Laser energy was applied through a rigid bronchoscope using a conventional bronchoscopic coupler or through a prototype CO_2 waveguide (Heraeus LaserSonics).[9]

Methods of anesthesia, safety precautions, and monitoring have been well described in the literature.[8,10] We prefer intravenous general anesthesia, muscle relaxation, and controlled Venturi ventilation for most high-grade central obstructions. Smaller lesions are treated under topical anesthesia and intravenous sedation permitting spontaneous ventilation. Our technique of endoscopic laser treatment is modified from that of Dumon and has been described elsewhere[10] (Figs 2 and 3). Initially, a malignant lesion was extensively photocoagulated with multiple laser applications using the noncontact technique. When the lesion appeared adequately photocoagulated, it was resected with the tip of the rigid bronchoscope and was removed with suction or biopsy forceps. Benign lesions, such as tracheal stenoses, were partially vaporized by making radial incisions with the CO_2 or Nd:YAG laser — usually the former — and then were further dilated with the rigid bronchoscope.

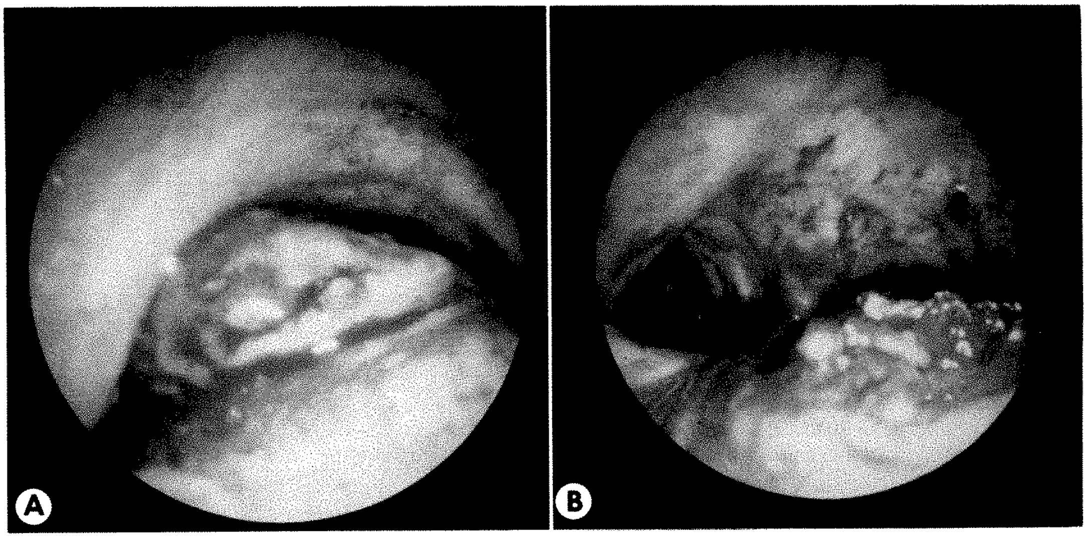

Fig 3. Endoscopic views in 64-year-old man with large cell carcinoma that obstructed trachea and resulted in respiratory failure, intubation, and mechanical ventilation. A) Preoperative. B) Distal trachea immediately after neodymium:yttrium-aluminum-garnet laser bronchoscopy. Patient was extubated 24 hours after operation.

TABLE 1. NATURE OF OBSTRUCTION AND MAJOR SYMPTOMS

	No. of Patients	*No. of Operations*	*Sex (M:F)*	*Mean Age (y, M:F)*	*Main Symptoms*			
					Dyspnea	*Hemoptysis*	*Cough*	*Postobstructive Pneumonitis*
Lung cancer	200	270	132:68	67:63	220	34	9	7
Metastatic cancer	36	55	19:17	63:62	46	7	2	0
Benign tumors	6	16	3:3	51:48	15	0	1	0
Stenosis	27	59	14:13	57:63	49	8	2	0
Total	269	400	168:101	65:62	330	49	14	7

RESULTS

The causes of obstruction and the sex, age, and symptoms of the patients treated are listed in Table 1. The majority of our patients (200) had stage III carcinoma of the lung. Metastatic tumors produced the airway obstruction in 36 patients. Dyspnea was, by far, the most common indication for operation and was the primary symptom in two thirds of the patients. The cell types of the malignant tumors are listed in Table 2. The distribution of the lesions in the tracheobronchial tree is shown in Fig 4. The number of patients treated for benign conditions and the results obtained in patients treated with the CO2 laser are detailed in Table 3.

Of the 367 procedures in the operating room, the rigid instrument was used in 327 operations; the flexible bronchoscope was used in 16 procedures. Both bronchoscopes were used in 24 procedures. General anesthesia was employed in 319 procedures, and local anesthesia was used in 48 operations. Venturi jet ventilation was used in 302 procedures. In 33 operations, patients breathed spontaneously with assistance by Venturi jet ventilation when needed. The mean operative time was 52 minutes, and the mean anesthesia time was 85 minutes.

Significant relief of symptoms was reported by the patients after 313 (78.3%) of the 400 procedures. In nearly all instances, physical examination and performance status confirmed the subjective impression. No change in the severity of symptoms was reported after 87 procedures (21.8%). Of the 16 patients who required preoperative mechanical ventilation, 6 were weaned successfully after laser therapy. Immediate anatomic improvement of the obstruction was achieved after 327 procedures (81.8%), whereas no improvement in the caliber of the lumen of the airway occurred in the rest. Preoperative radiography of the chest showed partial or total atelectasis in 137 patients. Postoperatively, radiography showed an appreciable degree of reexpansion in 70 patients (51%).

Complications were few. Those that occurred during the operation, during the recovery room period, and up to discharge of the patient are listed in Table 4. One death occurred in the operating suite (operative mortality rate, 0.3%) and was a result of acute tension pneumothorax.

Two patients died of myocardial infarction during the first 48 hours after the operation. Another

TABLE 2. HISTOLOGY OF MALIGNANT PRIMARY AND METASTATIC LESIONS AND PREVIOUS THERAPIES

Type of Lesion	*No. of Patients*	*No. of Operations*	*Sex (M:F)*	*Mean Age (y, M:F)*	*Previous Surgical Resection*	*Previous External Irradiation*	*Previous Chemotherapy*
Primary							
Squamous cell carcinoma	107	137	79:28	67:64	23	63	13
Adenocarcinoma	24	40	12:12	63:61	7	12	8
Large cell carcinoma	40	60	25:15	65:60	3	22	6
Small cell carcinoma	16	16	9:7	66:63	2	10	7
Adenoid cystic carcinoma	3	4	2:1	61:68	1	1	0
Carcinoid tumor	6	9	4:2	78:0	2	0	0
Other	4	4	2:2	77:61	2	2	0
Total	200	270	133:67	67:66	40	110	34
Metastatic							
Renal cell	12	22	10:2	66:61	9	7	6
Colon	7	12	2:5	64:68	3	2	4
Gastric	1	1	0:1	0:63	1	0	1
Esophagus	7	10	4:3	67:62	4	5	0
Breast	3	4	0:3	0:66	2	2	2
Endometrium	1	1	0:1	0:64	0	1	0
Ovary	1	1	0:1	0:39	0	1	1
Thyroid	1	1	0:1	0:53	1	1	0
Melanoma	1	2	1:0	44:0	1	1	0
Ameloblastoma	1	1	1:0	37:0	1	1	0
Larynx	1	1	1:0	57:0	1	1	1
Total	36	56	19:17	56:60	23	22	15

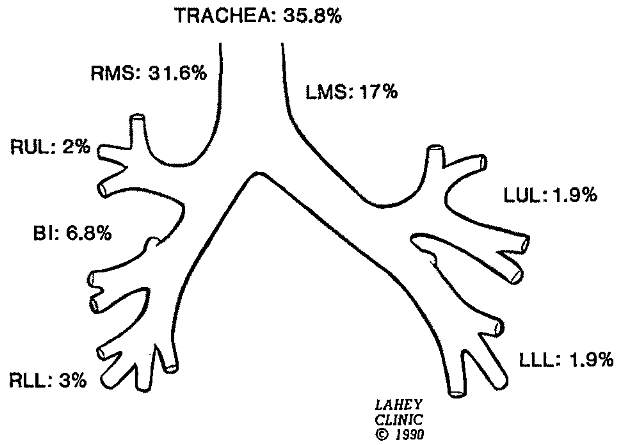

Fig 4. Anatomic distribution of treated obstructive lesions in tracheobronchial tree. (By permission of Lahey Clinic.) RMS — right main stem bronchus, RUL — right upper lobe bronchus, RLL — right lower lobe bronchus, LMS — left main stem bronchus, LUL — left upper lobe bronchus, LLL — left lower lobe bronchus, BI — bronchus intermedius.

patient with severe airway obstruction from external compression died on the first day after operation. A total of 11 patients died within 1 week after the procedure. The causes of death were myocardial infarction (3 patients), cancer obstructing the airways (4 patients), generalized cancer (1 patient), pneumothorax (1 patient), and massive hemoptysis (1 patient). Another patient died 3 days after discharge of unknown cause.

The overall survival of the patients with malignant diseases is depicted in Fig 5. Treatment employed after laser treatment is detailed in Table 5. More than one treatment was needed in 47 patients with malignant lesions. Endobronchial brachytherapy with low-dose-rate iridium 192 was given to 41 patients. A few patients received palliative chemotherapy.

Immediate relief from symptoms of obstruction of the airway occurred after 48 procedures (81.3%) for benign stenosis. Eight patients received repetitive laser therapy. No deaths or severe side effects occurred in patients with benign disease.

In 12 procedures for benign tumors, laser therapy improved airway obstruction and resulted in relief of symptoms. In four patients, no improvement occurred. Subsequent laser treatments were required in three patients.

DISCUSSION

The epidemic of carcinoma of the lung during the last two decades has resulted in many patients presenting with malignant lesions obstructing the central airways. These patients are often extremely symptomatic with profound dyspnea, uncontrolled hemoptysis, or postobstructive sepsis. The majority of patients presenting with lesions obstructing the central airways have tumors that are inoperable because of mediastinal involvement or lesions that are too central for surgical resection. Chemotherapy has proved inadequate for the treatment of such patients. Traditionally, most patients have been referred for external beam radiotherapy for control of endobronchial disease. Some studies,[11,12] however, have suggested that external beam radiotherapy is inadequate treatment for patients with bulky endobronchial tumors. Saunders et al[11] demonstrated that 95% of patients treated with radiotherapy had evidence of persistent or recurrent tumor at the primary site at the time of autopsy. Many patients showed no evidence of distant metastasis. Chetty et al[12] also noted a high incidence of persistent endobronchial disease in patients treated with external beam radiotherapy for lesions obstructing the large airways. These authors[11,12] suggested that local therapy might better relieve endobronchial obstruction while producing less toxicity.

The introduction of laser technology in bronchology has proved to be an important addition to the management of patients with endobronchial obstruction. Unlike ionizing radiotherapy, laser therapy may be used repeatedly for the palliation of malignant tracheobronchial obstruction. Classic papers by Toty et al[3] and Dumon et al[5] described the technique of Nd:YAG laser therapy for patients with malignant endobronchial obstruction and attested to the safety and effectiveness of this therapy. Brutinel et al,[13] in a series of 116 patients with 176 laser applications, indicated that the quality and duration of life were improved in patients with obstructing carcinoma who were treated with laser bronchoscopy. Although the CO2 laser was the initial laser employed for tracheobronchial laser therapy,[2] its use in the treatment of patients with malignant obstruction should be abandoned because of the poor hemostatic properties of this laser's wavelength. The hypervascularity of many malignant endobronchial neoplasms is best treated with the Nd:YAG laser because of its excellent coagulation properties.[14]

The CO2 laser still has an important role in tracheobronchial laser therapy, because it remains ideal for patients with benign stenosis and tracheo-

TABLE 3. BENIGN LESIONS

Type of Lesion	*No. of Patients*	*No. of Operations*	*Sex (M:F)*	*Mean Age (y)*	*CO2 Laser*
Tumors					
Hamartoma	3	4	2:1	50	0
Fibroma	1	2	1:0	49	0
Papilloma	2	10	1:1	39	0
Total	6	16	4:2	46	0
Stenosis					
Granulation tissue	6	16	4:2	50	2
Fibrous	19	41	11:8	64	9
Other	2	2	0:2	59	0
Total	27	59	15:12	58	11

TABLE 4. COMPLICATIONS (NUMBER OF PROCEDURES)

Complication	*Operating Room*	*Recovery Room*	*After Recovery Room*	*Total*	*Fatal Outcome*
Cardiovascular					
Arrhythmias	3	5	10	18	0
Myocardial infarction	0	0	3	3	2
Hemorrhage	1	0	1	2	0
Hypotension	2	1	0	3	0
Pericarditis	0	0	1	1	0
Pulmonary edema	0	1	0	1	0
Respiratory					
Bronchial obstruction	0	0	3	3	0
Refractory hypoxemia	6	2	0	8	0
Pneumothorax	1	0	1	2	1
Bronchospasm	0	1	3	4	0
Respiratory failure	0	3	5	8	1
Other					
Fever	0	0	3	3	0
Laryngospasm	1	0	0	1	0
Total	14	13	30	57	4
Percent	24.6	22.8	52.6	100	7

bronchial papillomatosis.[15] The excellent cutting and vaporization qualities of the CO_2 laser energy permit discrete resection of benign stenosis with minimal damage to the airway wall.[14,16,17] Central airway papillomas can undergo vaporization with the CO_2 laser with minimal bleeding.

Our experience with Nd:YAG laser bronchoscopy is similar to that of larger series from other institutions.[5,6,10,13,18-21] Primary or metastatic malignant lesions were responsible for tracheobronchial obstruction in 90% of our patients. All patients had symptoms severe enough to warrant urgent therapy. Only 10% of our patients had benign lesions.

Squamous cell carcinoma was the most common cell type of the primary lung neoplasms treated. This has been the experience of others[19] and reflects the central nature of this tumor, which often arises at the level of the lobar bronchi. Endobronchial metastatic renal cell carcinoma was the most common metastatic lesion in the patients we treated (Table 2).

Another frequently occurring metastatic lesion was carcinoma of the esophagus. This tumor produced obstruction of the central airways by direct extension from the primary tumor or from local mediastinal nodes rather than by hematogenous spread as seen in the other metastatic cancers.

Our philosophy regarding indications and techniques of therapy is similar to that outlined by Dumon.[22] For the most part, we have treated patients with central lesions because these lesions produce severe symptoms that warrant therapy despite the inherent risks of the procedure. We employed the rigid bronchoscope in 88% of our procedures because we believe this instrument offers a number of advantages over the flexible bronchoscope,[10] including better control of hemorrhage because of the use of large suction catheters, assurance of ventilation with the Venturi jet, excellent visualization because of the high quality optics of the telescope, and rapid removal of tumor through the open tube with large biopsy forceps. The flexible bronchoscope was often a helpful tool when used through the rigid bronchoscope. For the treatment of patients with highly vascular and bulky tumors, however, we believe that the flexible bronchoscope is not adequate. The flexible bronchoscope was, however, useful in the outpatient bronchoscopy suite for the treatment of patients with small lesions. Patients treated with this method had mild, noncritically obstructing tumors that required photocoagulation for hemoptysis or had benign lesions, such as papillomas or suture granulomas.

The anesthetic management of patients who require laser bronchoscopy is challenging to the anesthesiologist and the endoscopist. Multiple anesthesia techniques are available for use with rigid bronchoscopy. Our technique is similar to that of Duckett et al.[23] In high-risk patients or in elderly patients, we usually attempt to carry out the procedure with topical lidocaine, intravenous sedation, and assisted ventilation. However, with this topical technique, control of cough is often difficult.

The operative times for patients with malignant lesions were initially between 37 and 89 minutes. As our experience increased, the operative time dropped to a range of 30 to 40 minutes. This shorter time is in contrast to operative times lasting several hours that have been reported[13] when the flexible bronchoscopic technique is used.

Our operative mortality rate compares favorably with that described by Dumon[22] in a larger series of patients from several institutions. The majority of

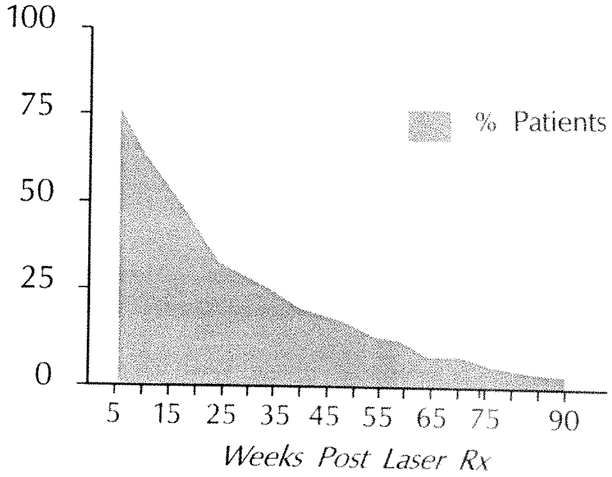

Fig 5. Survival of patients with malignant lesions. Rx — therapy.

TABLE 5. TREATMENT AFTER LASER THERAPY

Type of Carcinoma	*Brachytherapy*	*Repeat Laser Therapy*	*Operation*	*Chemotherapy*	*External Beam Irradiation*
Squamous cell carcinoma	18	14	1	2	0
Adenocarcinoma	9	9	0	2	0
Small cell carcinoma	1	0	0	3	0
Large cell carcinoma	8	12	1	2	0
Metastatic carcinoma	5	12	1	2	0
Total	41	47	3	11	0

deaths in the first week after operation were related to the presence of coronary artery disease, chronic obstructive airway disease, or an extensive underlying malignant lesion. Our one intraoperative death was the result of tension pneumothorax, possibly related to rupture of an emphysematous bulla by the Venturi jet ventilation system.

Survival data are difficult to interpret in this group of patients with advanced carcinoma. A prospective controlled study would be impossible with this group of patients. Brutinel et al[13] employed a group of historical controls at the Mayo Clinic and noted a favorable survival rate in patients treated with Nd:YAG laser bronchoscopy. The survival curve of patients with carcinoma seen in Fig 5 is impressive, considering the fact that many of our patients presented in extremis and would have died of suffocation within days. Of the 16 patients who were in respiratory failure and intubated at presentation, 40% could be extubated after laser bronchoscopy. The remaining patients who were intubated had tumors that were too extensive for laser bronchoscopy or that obstructed the airway by external compression. Brachytherapy and photodynamic therapy added to laser therapy can prolong relief from airway obstruction in selected patients.[24,25]

In summary, our experience in treating 269 patients with 400 bronchoscopy procedures using the Nd:YAG laser and the CO2 laser represents the superb capabilities of these lasers in providing palliation for patients with obstruction of the central airway resulting from malignant tumors and for patients with selected benign stenoses. Our intraoperative mortality rate of 0.3% attests to the relative safety of this procedure. We believe both the Nd:YAG laser and the CO2 laser should be applied through rigid bronchoscopes. Our preferred anesthesia technique involves intravenous general anesthesia with muscle relaxation and Venturi jet ventilation. Selected patients can be treated after receiving topical anesthesia and sedation by means of either the rigid or flexible bronchoscope to deliver the laser energy to the lesion obstructing the airway.

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OBJECTIVE VOICE MEASUREMENTS & STANDARDS

A course entitled Objective Voice Measurements & Standards will be held July 22-23, 1991, at the Warwick Hotel in Philadelphia, Pennsylvania. For further information, contact The Voice Foundation, 1721 Pine Street, Philadelphia, PA 19103; (215) 735-7999.

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AMERICAN AUDITORY SOCIETY, INC

The 18th annual meeting of the American Auditory Society will be held September 22, 1991, in Kansas City, Missouri. For further information, contact Don W. Worthington, PhD, Chair, AAS Program Committee, Boys Town National Institute, 555 North 30th Street, Omaha, NE 68131.

Ann Otol Rhinol Laryngol 100:1991

MICROTRAPDOOR FLAP REPAIR OF LARYNGEAL AND TRACHEAL STENOSIS

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Twenty patients have undergone repair of laryngeal and tracheal stenosis by microtrapdoor accessing of scar or soft tissue and removal with the carbon dioxide laser. A total of 34 flap procedures were performed in the 20 patients. Follow-up ranged from 8 months to 4 years, and 30 of these flaps were considered successful on the basis of improvement of the airway. The only complications were postoperative granulation tissue in 2 patients that responded to endoscopic removal.

KEY WORDS — laryngeal stenosis, microtrapdoor flap, tracheal stenosis.

INTRODUCTION

Laryngotracheal stenosis is a difficult clinical problem, as evidenced by the large variety of procedures used for its repair. Laser epithelial preservation techniques were pioneered by Dedo and Sooy,[1] using the carbon dioxide (CO_2) laser to develop a microtrapdoor (MTD) flap to preserve mucosa in the posterior glottis, subglottis, and trachea. This procedure utilizes the accuracy and tissue preservation capabilities of the CO_2 laser to develop a mucosal trapdoor for the removal of stenotic scar. Upon completion of the procedure, the microtrapdoor flap can provide mucosal coverage of the area to prevent further stenosis.

A report from our institutions by Duncavage et al[2] in 1987 involved six patients, all of whom had improved airways after the MTD flap procedure. The purpose of this paper is to report on our continued experience with this technique and to provide longer follow-up information on our previous series.

MATERIALS AND METHODS

A retrospective review was conducted of all patients with laryngeal and tracheal stenosis treated from June 1985 to January 1990 with the MTD flap technique. The CO_2 laser MTD flap is indicated for thin stenoses, 10 mm or less in vertical height, involving the posterior commissure, subglottis, and trachea. All adult patients meeting the criteria during the study period underwent the procedure. Consecutive pediatric cases meeting the criteria were recruited between July 1987 and January 1990. This review includes six patients presented in our previous report. The cases were reviewed from the standpoint of age, sex, location of stenosis, cause of the stenosis, tissue characteristics of the stenosis, previous treatments, presence of tracheotomy at the time of MTD, ultimate result, ability to decannulate the patient, and duration of follow-up. A successful outcome was defined as an improved airway on endoscopic observation, relief of dyspnea, and decannulation when applicable. The surgical technique of the MTD flap has been detailed in a previous report.[2]

RESULTS

Twenty patients underwent the CO_2 laser MTD flap procedure between 1985 and 1990 (see Table). This group consisted of 8 children from 11 months to 15 years old and 12 adults from 22 to 67 years. The pediatric patients included 1 infant, 4 children, and 3 teenagers. There were 5 boys and 3 girls in the pediatric group and 6 women and 6 men in the adult group.

In the pediatric group, three had acquired neonatal circumferential subglottic stenoses of mature scar. Two had congenital circumferential subglottic stenoses, one having soft redundant mucosa, and the other being firm submucosally with a pinpoint lumen. The three older children were treated for acquired traumatic or intubation lesions, two of which were tracheal and one of which was located in the posterior commissure (see Table).

In the adult group, four patients had glottic, three had subglottic, and five had tracheal stenosis. Three of four patients with glottic stenosis had isolated posterior commissure lesions, and one had both anterior and posterior glottic involvement. Two of these glottic lesions resulted from endotracheal intubation, one lesion resulted from lye ingestion, and one was secondary to scarring after arytenoidectomy and cordectomy. Two of three subglottic stenoses were idiopathic (one patient had documented and the other suspected gastroesophageal reflux) and the third resulted from cricothyrotomy. Three of five tracheal stenoses were at previous tracheotomy sites and two resulted from intubation injuries (one at the site of a compressive goiter). With the exception of the two idiopathic soft subglottic

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.

REPRINTS — David J. Beste, MD, MACC Fund Research Center, 8701 W Watertown Plank Rd, Milwaukee, WI 53226.

MICROTRAPDOOR FLAP OF LARYNGEAL AND TRACHEAL STENOSIS

Pt No.	*Age*	*Sex*	*Stenosis Location*	*Tissue Type*	*Cause*	*Previous Procedures*	*Tracheotomy*	*No. of Flaps*	*Flaps Staged*	*Airway Improved*	*Decannulated*	*Successful*
1	11 mo	M	Subglottis (circ)	Mature	Congenital	None	Yes	2	Yes	Yes	No	No
2	16 mo	F	Subglottis (circ)	Soft, redundant	Congenital	Laryngotracheoplasty	Yes	2	Yes	Yes	Yes	Yes
3	16 mo	F	Subglottis (circ)	Mature	Neonatal intubation	None	Yes	3	Yes	Yes	No	No
4	18 mo	M	Subglottis (circ)	Mature	Neonatal intubation	None	Yes	2	Yes	Yes	No	No
5	22 mo	F	Junction subglottis and trachea	Mature	Neonatal intubation	None	Yes	2	Yes	Yes	No	No
6*	12 y	M	Posterior commissure	Mature	Blunt trauma, intubation	Dilation, ILS, laser excision x4	Yes	1	NA	Yes	Yes	Yes
7	13 y	M	Tracheal	Mature	Intubation	Multiple granulation tissue excisions, dilations, ILS	No	3	Yes	Yes	NA	Yes
8	15 y	M	High tracheal	Mature	Intubation	Multiple dilations, ILS, T-tube	Yes	2	Yes	No	No	No
9	22 y	F	High tracheal	Mature	Tracheotomy	Silastic sheet roll stent	Yes	2	Yes	Yes	Yes	Yes
10*	26 y	M	High tracheal (circ)	Mature	Intubation	Multiple laser excisions of granulation tissue, dilations	Yes	1	NA	Yes	Yes	Yes
11	28 y	M	Anterior and posterior commissure	Mature	Intubation	L and R laser arytenoidectomy	Yes	2	No	Yes	Yes	Yes
12*	56 y	F	Posterior commissure, R arytenoid fixation	Mature	Intubation	None	Yes	1	NA	Yes	Yes	Yes
13	62 y	F	Tracheal	Mature	Intubation, goiter	Tracheal resection, anastomosis	Yes	2	No	Yes	Yes	Yes
14*	42 y	M	Subglottis	Soft	Idiopathic	None	Yes	2	Yes	Yes	Yes	Recurrence
15*	58 y	F	Junction subglottis and trachea	Soft	Idiopathic	Multiple dilations, ILS	Yes	1	NA	Yes	Yes	Yes
16	63 y	M	Tracheal	Mature	Tracheotomy	None	Yes	1	NA	Yes	Yes	Yes
17	63 y	M	Tracheal	Mature	Tracheotomy	Granulation tissue excision, ILS, laser evaporation	No	1	NA	Yes	NA	Yes
18	45 y	M	Anterior subglottis	Mature	Cricothyrotomy	T-tube	Yes	1	NA	Yes	Yes	Yes
19	67 y	F	Posterior commissure	Mature	Arytenoidectomy, cordectomy	Arytenoidectomy, L partial cordectomy	Yes	2	Yes	Yes	Yes	Yes
20*	30 y	F	Posterior commissure, R arytenoid fixation	Mature	Lye ingestion	None	Yes	1	NA	Yes	No	Yes

ILS — intralesional steroid injection, circ — circumferential, NA — not applicable.
*Previously reported by Duncavage et al.[2]

stenoses, these stenoses were all mature hard scar.

Eighteen patients had a tracheotomy present at the time of the MTD flap. Two patients, one adult and one teenager, did not require a tracheotomy at the time of the MTD flap procedure. Patient 7, with a short tracheal stenosis secondary to an endotracheal tube, did not require a tracheotomy but suffered from moderate to severe dyspnea on exertion that restricted activity. Patient 17, with a short tracheal stenosis, had an insignificant tracheocutaneous fistula that was not used as an airway. In these two cases, the MTD flap was performed with the ventilating bronchoscope coupled to the CO2 laser.

Eight patients (4 adults and 4 children) received no previous surgical procedures for their stenoses, while 12 patients failed previous surgical therapies (see Table). The 8 pediatric patients had a total of

17 MTD flaps, all except 1 having staged flaps (see Table). The procedures in five congenital and acquired neonatal stenosis cases were performed as staged outpatient procedures, with each flap encompassing one third of the circumferential stenosis. The MTD flaps resulted in an increased intraluminal diameter, but there was insufficient improvement for decannulation in 4 of 5 patients. Two patients, 11 and 16, have undergone laryngotracheoplasty with costal cartilage grafting and subsequently been decannulated. Patient 8 failed to improve after two staged MTD tracheal flaps; he was decannulated after laryngotracheoplasty.

In patient 2, with the soft redundant mucosal stenosis, two staged MTD flaps were successful. Patient 6 responded successfully after a single MTD flap to the posterior commissure. Patient 7 underwent three staged MTD bronchoscopic laser flaps and the treatment was successful enough to allow participation in school sports over the last 9 months.

The 12 adults in this series had a total of 17 MTD flap procedures (see Table). Seven patients underwent a single flap procedure. Two patients underwent a single procedure with two MTD flaps performed simultaneously. Three patients underwent two staged flaps. Two patients had additional procedures simultaneous to the MTD flap. A large MTD flap encompassing a laser arytenoidectomy was performed for patient 12, who had arytenoid fixation. An Evans rolled Silastic stent was placed for patient 13, who had a severe stenosis after a tracheal resection and anastomosis.

Eleven of the 12 adult patients were successfully treated with the MTD flap, with success being defined as an improved airway on observation, relief of dyspnea, and decannulation when applicable. The range of follow-up in the successfully treated patients ranged from 8 months to 48 months. The mean follow-up was 24 months, and the median follow-up was 26 months.

The only complications were postoperative granulation tissue in two patients that responded to endoscopic removal.

Of the six patients previously reported by Duncavage et al,[2] one was lost to follow-up, one had recurrence of a subglottic stenosis, and four have continued to do well. Patient 20, despite an improved airway and decannulation for several months, had the tracheotomy replaced for chronic aspiration secondary to an associated hypopharyngeal stenosis. Patient 14, who was included as a success in our last review, developed a recurrence of his subglottic stenosis 8 months after successful decannulation. Ultimately, he was successfully decannulated after an open scar excision, mucosal grafting, and a hyoid interposition graft performed at another institution.

DISCUSSION

The MTD mucosal flap must remain viable after manipulation in order to provide epithelial coverage. The flap should be thin enough for manipulation but not to the point of embarrassing the blood supply. The inferior border needs to be sufficiently wide to support blood flow after the lateral incisions. The lateral incisions cause the MTD mucosal flap to contract, resulting in a small U-shaped area of raw scar that undergoes rapid reepithelialization. It has not been necessary to have the flap lie down immediately. The initial presentation of fibroblast and flap contraction will provide approximation to the raw surface.

A tracheal stenosis in a 5-year-old boy was the one failure reported by Dedo and Sooy.[1] This patient had a small tracheal diameter (4 mm) and a long scar (6 to 10 mm). Similarly, our success in children less than 5 years of age was poor, with only one of five cases successful. The one successful MTD flap procedure in a child under 5 was patient 2, with a soft congenital subglottic stenosis. She had an adequate lumen after laryngotracheoplasty, but failed secondary to soft redundant mucosa filling the subglottic lumen.

The MTD flap technique is indicated in small stenoses with a length of 10 mm or less. A tracheotomy is necessary when a flap is greater than 4 mm in length in adults and teenagers and in all children. In cases of stenoses associated with arytenoid fixation or vocal cord paralysis, a wide flap can be used to include arytenoidectomy and partial submucous cordectomy.

An alternate mucosa-preserving laser technique was introduced by Shapshay et al.[3] They reported on five patients with severe fibrotic subglottic and upper tracheal stenosis. These patients were treated by endoscopic radial laser incisions and dilation using both CO_2 and neodymium:yttrium-aluminum-garnet lasers. Their technique involved radial laser incisions of the circumferential scar tissue that released the cicatrix or bandlike stenosis, followed by gentle dilations. The small bridges of remaining epithelium were helpful in preventing recurrence of the stenosis.

In conclusion, the CO_2 laser MTD flap is a successful technique for repair of thin stenoses, 10 mm or less, in the posterior commissure, subglottis, and trachea. It can be an effective procedure after a variety of other techniques have been attempted. Flaps wider than 4 mm will require a tracheotomy. The present technique is not as effective in pediatric patients with hard stenoses.

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SIXTH WORLD CONGRESS IN ULTRASOUND

The Sixth World Congress in Ultrasound will be held September 1-6, 1991, in Copenhagen, Denmark. For further information, contact Spadille Congress Service ApS, Sommervej 3, DK-3100 Hornbaek, Denmark; telephone 45 2 202496, telefax 45 2 200160.

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INTERNATIONAL HEARING AID CONFERENCE: SIGNAL PROCESSING, FITTING, & EFFICACY

The International Hearing Aid Conference: Signal Processing, Fitting, & Efficacy will be held June 21-23, 1991, at The University of Iowa, Iowa City, Iowa. The organizing committee includes Richard S. Tyler, PhD (Signal Processing), Chaslav V. Pavlovic, PhD (Fitting), and Ruth A. Bentler, PhD (Efficacy). Further information may be obtained from any member of the organizing committee at the Department of Speech Pathology and Audiology, The University of Iowa, Iowa City, IA 52242; (319) 335-8726, FAX (319) 335-8851.

Ann Otol Rhinol Laryngol 100:1991

IMAGING CASE STUDY OF THE MONTH

ETHMOIDAL CHOLESTEATOMA

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Cholesteatoma, also known as a keratocyst, epidermoid, epidermal cyst, epidermal dysembryodysplasia, cholesterol granuloma, or keratoma, is mostly seen in the temporal bone. Cholesteatomas have been described outside the temporal bone in the kidney, testicle, skin, breast, central nervous system, cranial vault, orbit, mandible, and paranasal sinuses. In the paranasal sinus a cholesteatoma is most often found in the frontal sinus; it is rarely found in the ethmoid cells and very rarely in the maxillary sinus.[1-4]

The epidermoid tumor was first reported by Pinson in 1807. In 1829 Cruveilhier described cholesteatoma as a "pearly tumor" by virtue of its highly refractive and nodular surface. The term cholesteatoma was introduced by Muller in 1833 because of the presence of cholesterol crystals.[2-4] In 1916 Haeggstrom first reported a frontal sinus cholesteatoma, and later other cases followed.[4]

Four basic theories of pathogenesis may explain the development of this unusual lesion. The first is a congenital origin from the neural groove closure during the fifth embryonic week. The second theory is the entrance of epithelium directly with the effect of trauma. Another theory relates metaplasia of the epithelium to the effects of chronic infection. The fourth is the immigration theory, in which the epithelium would migrate from the nasal vestibule.[1-4]

CASE REPORT

A 16-year-old girl was admitted to our clinic in December 1987, complaining of painful, progressive swelling of the right eye. Upon examination, the right eye showed proptosis and was displaced laterally. The movements of the eye were restricted. A soft, tender mass, rubberlike in consistency, was palpated along the right medial orbital rim. Fundoscopic examination revealed atrophic and pigmented areas on the peripheral retina in both eyes. Her corrected vision was 3/10 on both sides.

Plain film examination demonstrated an expanded right ethmoid sinus with a dense cortical border (see Figure, A). Axial computed tomography with a soft tissue window (see Figure, B) revealed an expanded right ethmoid sinus. A magnified view through the middle of the orbit (see Figure, C) showed an ethmoid mass and proptosis. Sinus septae hypertrophy was present peripherally, and the upper nasal fossa was narrowed medial to the lesion. A coronal computed tomographic view (see Figure, D) confirmed proptosis, right ethmoid sinus enlargement, and upper nasal fossa compressive change. The sinus border was thickened and septum hypertrophy was present.

The patient underwent an exploratory operation through a lateral rhinotomy. No cyst wall was identified, but pearly grey epithelium layers were present. The mass was composed of a whitish yellow cheesy material that had a fetid odor. The possibility of cholesteatoma was suspected at this stage of the operation.

After the removal of this material it was seen that the trabecula between the anterior and posterior ethmoidal air cells and the anteroinferior wall of the frontal sinus were eroded. A large cavity was formed with smooth margins. There was a large bony defect in the roof of the orbit, but the inner table of the frontal bone seemed to be intact. There was an opening in the medial wall of the cavity communicating with the nasal cavity. A polyethylene tube was inserted to ensure the drainage of the sinuses through the nose.

Postoperatively, lincomycin hydrochloride was given in accordance with the results of a culture sensitivity test that was performed on a sample taken during the operation.

PATHOLOGIC FINDINGS

The removed specimen was composed of cheesy material and epithelial layers. Microscopically, it had an outer capsule, an inner squamous epithelial lining with prickle cells, and an accumulation of keratin. There was diffuse edema and mild chronic inflammation of the submucosa. Interposed areas of cholesterol granuloma were present (see Figure, E). The patient's postoperative vision and eye mobility were within normal limits and there was no proptosis. There has been no evidence of recurrence over the past 26 months.

DISCUSSION

The precise origin of sinus cholesteatoma has

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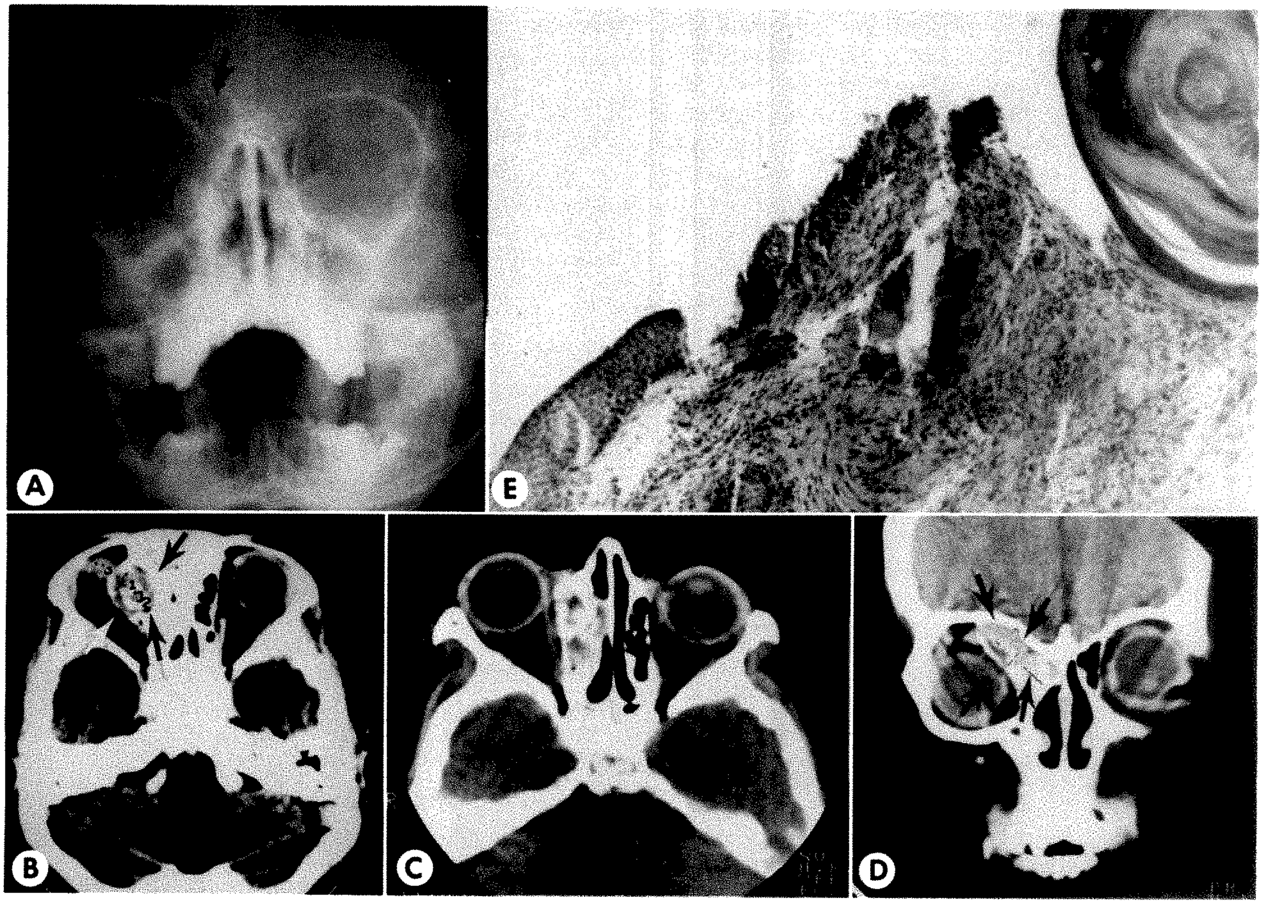

Ethmoidal cholesteatoma. A) Waters view with expansile right ethmoid sinus mass. B) Axial skull computed tomogram with soft tissue window showing right ethmoid sinus expansion. C) Axial sinus computed tomogram with bone window showing expanded right ethmoid sinus mass producing proptosis and nasal fossa compression. Some trabecula thickening along sinus margin is present. D) Coronal view showing globe displacement. Thick wall of expanding ethmoid lesion is well defined. E) Typical histopathology of cholesteatoma showing mild inflammation beneath keratinizing squamous epithelium and lamellar keratin on right (H & E, original x32).

been discussed in the literature. Ramsey et al[5] have emphasized the importance of a traumatic history in several cases. They suggested that a small skin laceration at the time of trauma might serve for the introduction of epithelial elements.

Some authors have focused on metaplasia, migration, and congenital theories. In our case, there was no periorbital trauma, operation, or chronic sinusitis history. A congenital origin from epithelial remnants seems to be more likely in our case.

The mean age of diagnosis was 38 in the patients of Parke et al.[6] Beder et al[7] described a 13-year-old patient. Our patient was 16 years old.

Cholesteatoma will often produce proptosis. The diagnosis of frontal or ethmoidal cholesteatoma should be considered in the presence of any sort of swelling in this area, with or without orbital displacement or ocular dysfunction.[4,6-9]

The imaging characteristic of cholesteatoma is a sharply circumscribed bony defect with smooth marginal sclerosis. Margins of the defect will be scalloped because of slow erosion of the bone.[4,6-9]

In our case there was a right unilateral proptosis and a soft, tender, rubberlike mass that was palpated along the right medial orbital rim. Radiography revealed a mass with smooth sclerotic margins in the right ethmoid sinus. Expansile change was present. Computed tomography revealed a mass that compressed the nasal fossa and expanded into the orbit, producing lateral displacement of the globe.

Mucoceles, sebaceous cysts, fibromas, lipomas, osteomas, dermoid cysts, lacrimal sac tumors, and rare carcinomas must be considered in the differential diagnosis.

The effective treatment of cholesteatoma is surgical. The main aim should be to remove the surrounding wall of the cyst completely in order to prevent recurrence. In the treatment of frontoethmoid cholesteatoma, an osteoplastic flap via a brow or coronal incision, lateral rhinotomy, or lateral orbitotomy are the surgical approaches. If involvement of the inner table of the skull or dura is present, craniotomy may be necessary.[4,6,7,9]

Lateral rhinotomy was used in our case. The outer table of the frontal bone was destroyed. The lesion developed externally. The inner table of frontal bone was intact. On pathologic examination, the microscopic structures of the lesion were very typical and obvious (see Figure, E).

Recurrence can arise from incomplete removal of the lesion. If cosmetic reconstruction is necessary, it should be delayed for 1 year to ensure against recurrence.

In our case the cholesteatoma cyst was not very large. Therefore, there was no postoperative defect that would require any further reconstruction.

Osborn and Wallace[10] have reported a carcinoma associated with cholesteatoma and present a theory positing epidermoid cholesteatoma as a source of carcinoma. Consequently, we will follow up on the patient at 4-month intervals.

ACKNOWLEDGMENTS — We thank Ozgul Pasaoglu, MD, for pathologic examination and Zeki Ziylan, MD, for interpreting the computed tomography.

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INTERNATIONAL SYMPOSIUM ON GRAVES' OPHTHALMOPATHY

An International Symposium on Graves' Ophthalmopathy will be held Aug 23-24, 1991, in Amsterdam, the Netherlands. The symposium will bring together members from different disciplines interested in the management of Graves' ophthalmopathy. The program will include lectures, free communications, and posters on topics on surgical, medical, and radiotherapeutic management, on immunological aspects, and on classification of the eye changes. The deadline for submission of abstracts is June 1, 1991. For further information, contact Amsterdam Thyroid Club, c/o W. M. Wiersinga, MD, Dept of Endocrinology, F5-258, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

Ann Otol Rhinol Laryngol 100:1991

PATHOLOGY CONSULTATION

SINUS ASPERGILLOSIS AND ALLERGIC FUNGAL SINUSITIS

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Aspergillosis of the sinonasal tract has four basic clinicopathologic presentations depending on the mucosal or extramucosal involvement by the fungus. Two are saprophytic (aspergilloma and allergic *Aspergillus* sinusitis) and two are infectious (chronic indolent and invasive fulminant sinusitis). Tissue-invasive and angioinvasive aspergillosis can be a rapidly lethal disease, particularly in the immune-compromised host. The allergic form of paranasal sinus aspergillosis is presumed to be initiated by hyperreactivity to fungal antigens. Not all allergic fungal sinusitis is associated with *Aspergillus* species, and culture confirmation is necessary to distinguish the fungal agent. Surgical removal of the offending fungus is the mainstay of therapy in all forms of sinonasal aspergillosis and other fungal sinusitis. Antifungal agents and steroids complement surgical removal, depending on the form of the sinusitis.

Aspergillosis, and especially nosocomial *Aspergillus* infection, is becoming an important cause of morbidity and mortality. From 1970 to 1976 there was a 158% increase in the incidence of nosocomial aspergillosis in the United States that was associated with an increasing number of immunosuppressed patients.[1]

Saprophytic and ubiquitous in nature, *Aspergillus* species are normally only transient colonizers of humans. Airborne transmission is the principal route of transmission and the respiratory tract is the most common portal of entry. In nosocomial aspergillosis, pneumonia is the most common form of lower respiratory tract infection and *Aspergillus* sinusitis is the most common form of upper respiratory tract infection.[1] Definitive diagnosis of *Aspergillus* sinusitis is established by culture of an aspirate of the infected sinus or by culture of a nasal chamber in patients with radiographically compatible sinusitis. It must be appreciated, however, that fungal cultures will be negative in a considerable number of proven cases.[2]

In company with the general increase of nosocomial aspergillosis there is also an increase in aspergillosis of the sinonasal tract. This has been attributed to a heightened clinicopathologic awareness as well as host vulnerability brought about by compromise of the immune system.[3-6]

Stammberger et al[3] reported that *Aspergillus* species cannot actively penetrate undamaged and intact mucous membranes and skin, as they lack keratolytic enzymes. This finding accounts for separation of the four forms of *Aspergillus* involvement of the paranasal sinuses (Table 1) into two groups: extramucosal (saprophytic growth in retained secretions in a sinus cavity) and mucosal or penetrating fungal sinusitis. Each of the four forms has its own rather distinctive histopathologic findings as well as clinical and therapeutic implications.

Aspergilloma and allergic *Aspergillus* sinusitis are principally saprophytic and noninvasive. Chronic indolent sinusitis with aspergillosis is always potentially invasive — but it is invasive aspergillosis, in a fulminant or nonfulminant clinical course, that is destructive and often fatal. Fulminant disease is usually found in neutropenic patients with malignancies of the lymphoreticular or hematopoietic systems who are immune-suppressed.[6] Often beginning as an ulcerative necrosis of the nasal mucosa and destruction of the inferior turbinates, fulminant disease rapidly and progressively destroys the involved sinuses, manifests angioinvasion by the fungus, and extends into the orbit and brain. There is little tissue reaction to the tissue destruction, and

TABLE 1. *ASPERGILLUS* AND PARANASAL SINUSES

Type of Sinus Involvement	*Predisposition or Vulnerability*	*Extent of Involvement and Pathologic Changes*
Fulminant (invasive) sinusitis	Immunocompromised; associated lung disease common	Usually maxillary and/or ethmoids; significant nasal component; destructive, gangrenous necrosis; angioinvasion by fungus
Indolent, chronic sinusitis	Usually healthy host; no associated lung disease	Maxillary and/or ethmoids; active chronic inflammation
Aspergilloma	Usually healthy host or one with chronic sinus disease; posttraumatic; foreign body; no associated lung disease	Single sinus, usually maxillary; nonspecific chronic inflammation with cavitary "fungus ball"
Allergic *Aspergillus* sinusitis and allergic fungal sinusitis due to other fungi	Asthma with nasal polyps; atopic or healthy host; usually no associated lung disease	"Allergic" inspissated mucin ball or plug

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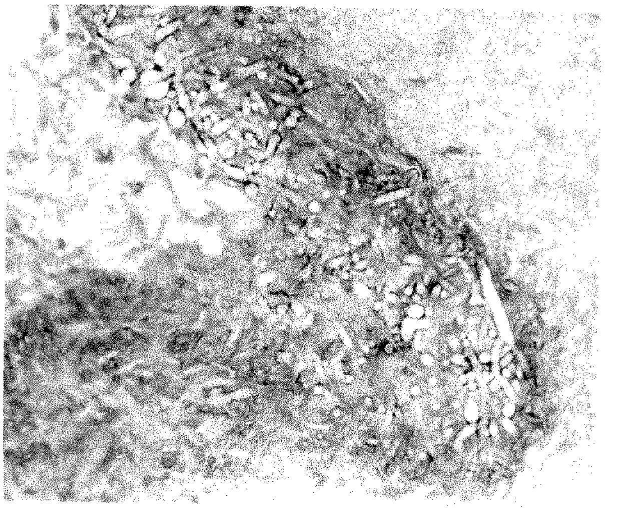

Fig 1. Aspergilloma (*Aspergillus* species confirmed by culture) of maxillary antrum with numerous entangled hyphae (H & E, original x400). Note absence of accompanying inflammation.

a granulomatous reaction is not seen. A granulomatous chronic inflammation, however, does accompany the more indolent form of sinusitis, and this can allow the infection to extend beyond the bony confines of the sinuses. An obvious immune deficiency is not usually found in chronic indolent *Aspergillus* sinusitis.[7]

Aspergilloma is an extramucosal fungus ball of aspergilli within a sinus, usually the maxillary antrum, that can provoke little or no inflammation (Fig 1). Typically, the fungal hyphae are arranged in concentric growth layers, much as they are on culture media. There may be conidiophores present, and with these a differential diagnosis of type of fungal disease is facilitated.

Instead of a fungus ball, the affected sinus in allergic *Aspergillus* or other allergic fungal sinusitis contains a firm, rubbery, and tenacious mucoid material in which there may be concreted debris. According to Katzenstein et al,[8] the diagnostic feature is an "allergic mucin," a pale eosinophilic or basophilic mucoid material in which are found eosinophils, sloughed epithelial cells, cellular debris, and Charcot-Leyden as well as other crystals (Fig 2A). Eosinophils in various states of preservation and number are often the preponderant cellular constituents. A distinctive, if not constant, laminar layering of the cells and cellular debris in the

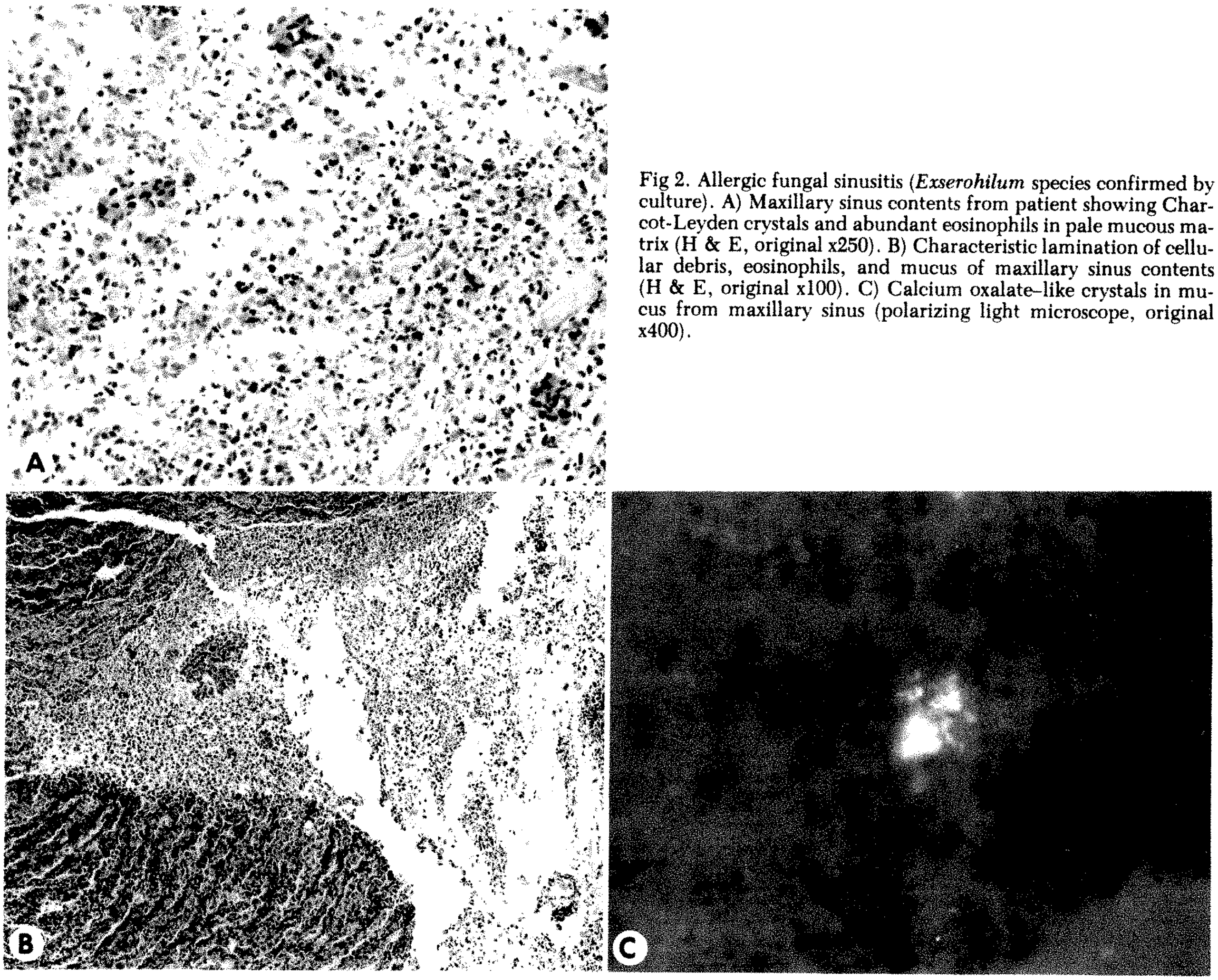

Fig 2. Allergic fungal sinusitis (*Exserohilum* species confirmed by culture). A) Maxillary sinus contents from patient showing Charcot-Leyden crystals and abundant eosinophils in pale mucous matrix (H & E, original x250). B) Characteristic lamination of cellular debris, eosinophils, and mucus of maxillary sinus contents (H & E, original x100). C) Calcium oxalate–like crystals in mucus from maxillary sinus (polarizing light microscope, original x400).

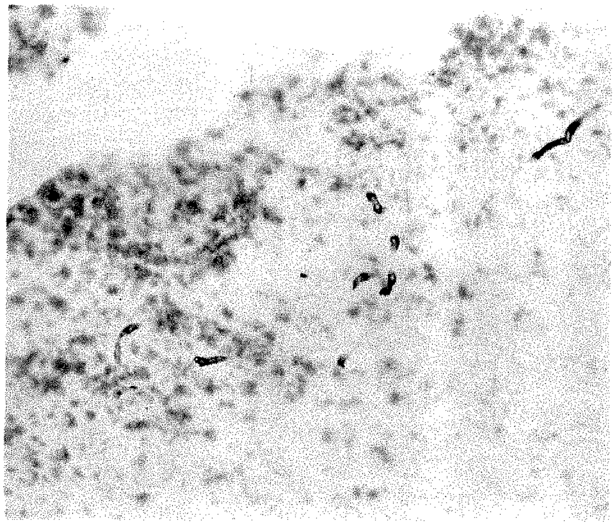

Fig 3. Fungal hyphae in allergic fungal (*Exserohilum* species) sinusitis (Gomori methenamine silver stain, original x250). Compare their sparsity to number of hyphae found in aspergillomas (Fig 1).

TABLE 2. CLINICAL FEATURES OF ALLERGIC *ASPERGILLUS* FUNGAL SINUSITIS

No. of patients	32
Sex of patients	19 F, 13 M
Age at presentation for therapy (y)	8-56
Patients with atopy	7
Patients with asthma	17
Patients with nasal polyps	28
Radiographic evidence of erosion of bone or expansion of sinuses	9
Involved sinuses*	
Maxillary	27
Ethmoid	26
Sphenoid	21
Frontal	13
Treatment	
Surgical	32
Topical steroids	10
Systemic steroids	6
Antifungal	8

Information from references 7, 8, 13-17.

*All reported cases had more than one sinus involved.

mucoid matrix should alert the pathologist to look for fungal hyphae (Fig 2B). There may be acute and chronic inflammatory cells, but invasion of tissues by the fungus is not seen. Birefringent crystals with the appearance of calcium oxalate are often seen in a spatial association with the fungal hyphae (Fig 2C).

Ease of finding fungal hyphae in each of the four types of clinical presentation depends on their number and preservation. The hyphae are most numerous in aspergillomas, and they are the most difficult to find in the chronic indolent, preinvasive form of sinusitis. In allergic *Aspergillus* sinusitis, hyphae are not numerous, and fungus balls are not seen (Fig 3). In any of the types of sinus involvement by *Aspergillus*, its septate and 45° angle dichotomous branching hyphae are best visualized with the use of silver impregnation stains such as a Gomori methenamine stain, but since other fungal hyphae can mimic *Aspergillus* in tissue sections, a definitive diagnosis cannot be made. The two species of *Aspergillus* most often confirmed by culture are *fumigatus* and *flavus*.

Confirmation by culture, supported by serum precipitins and immunoglobulin E specific for a given fungus, supersedes the subjective interpretation of *Aspergillus* species based on interpretation of the hyphal appearance in tissue sections. Of the 32 reported cases of allergic *Aspergillus* sinusitis, only 5 had culture confirmation. It is very likely, on the basis of an increasing number of case reports, that allergic (fungal) sinusitis is most often a consequence of fungal genera other than *Aspergillus*.[9-12] Because of this, limiting the diagnostic term to *Aspergillus* is inappropriate. We recommend the term "allergic fungal sinusitis," as used by Robson et al.[9]

DeFoer and associates,[5] in postulating an iatrogenic (maxillary sinus contamination during dental manipulations) alternate route of sinus infection by *Aspergillus*, and Jonathan et al[13] raise the likelihood of clinically overlooking noninvasive forms of *Aspergillus* sinusitis. The relatively recent recognition and description of the allergic form of sinus aspergillosis adds to that likelihood.

Table 2[7,8,13-17] presents demographic and clinical information on 32 patients with allergic *Aspergillus* sinusitis reported in the literature to date. As indicated above, it is likely that other fungi were responsible. Young adults are most often afflicted, and a history of asthma, atopy, and nasal polyposis is common. Clinical manifestations are those of a nonspecific recurrent or persistent sinusitis for several months or many years. The radiographic features of fungal sinusitis have been well reviewed by Zinreich et al,[18] and in that respect it is pertinent to point to the observation that 9 (28%) of the patients with allergic *Aspergillus* sinusitis manifested either an expansion or bone erosion of involved sinuses. Seven of the 9 patients were younger than 16 years of age. All 6 pediatric patients in the series reported by Manning et al[17] presented with facial deformities secondary to expansile sinusitis.

Clinical, pathologic, and immunologic findings in patients with allergic *Aspergillus* sinusitis have led to the proposal of a combination of type 1 (immunoglobulin E) and type 3 (immune complex) hyperreactivity to fungal antigens as the basis for the sinusitis.[7,14] This model is analogous to that proposed for allergic bronchopulmonary aspergillosis, even though none of the reported allergic sinusitis cases have involved well-documented pulmonary disease.[14,19]

The treatment of the extramucosal, noninvasive forms of fungal sinusitis is removal of the fungus and accompanying mucus, restoration of mucociliary drainage, and sinus ventilation. Surgical debridement and aeration with or without corticosteroids is the range of options for allergic extramucosal sinusitis. Antifungal agents are not advocated, as invasion does not occur in this condition. According to Waxman et al,[14] a proportion of patients with allergic *Aspergillus* sinusitis will be "cured" with a surgical procedure alone, another group will manifest recurrent disease within months, and another group will have recurrences after longer periods. Systemic steroids with subsequent long-term topical corticosteroids are employed for the last two groups. Further therapeutic principles have been reviewed by Goldstein et al.[7]

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EXTRACRANIAL OPTIC NERVE DECOMPRESSION MEETING

An Extracranial Optic Nerve Decompression Meeting will be held Nov 2-3, 1991, in Boston. For further information, contact Michael P. Joseph, MD, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114; (617) 573-3192.

LETTERS TO THE EDITOR

To the Editor:

We read with interest the paper by Drs Hsu, Zhu, and Zhao (Immunoglobulin E and Circulating Immune Complexes in Endolymphatic Hydrops, *Ann Otol Rhinol Laryngol* 1990;99:535-8). The authors conclude that "immediate-type allergy might play an important role in the cause of Meniere's disease." They also conclude that "some of the patients with Meniere's disease had an immune-complex-mediated type III allergy cause"; however, we believe that these conclusions cannot be drawn from the data presented.

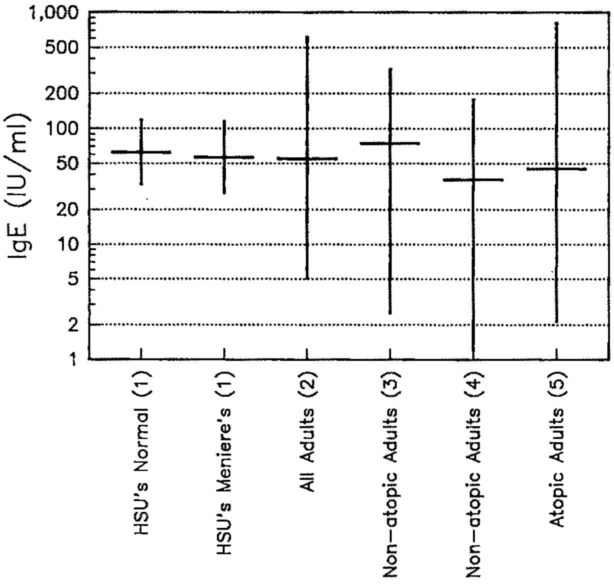
The report of this study is flawed by mistakes, omissions, and inappropriate analyses of the data. Further, the authors emphasize interpretations of the data that support their experimental hypothesis, reaching for some difference between experimentals and controls, rather than toward a rejection of the null hypothesis.

With regard to the serum IgE portion of the study, the IgE levels reported in their Fig 1 for both the normal subjects and the Meniere's patients are 10 times greater than those reported in several other series.[1-4] The data probably should have been subjected to a log transformation prior to analysis, since even the normal populations show extreme distribution ranges.

We assumed a tenfold correction factor and compared the IgE data in Hsu et al to data from the previously reported series. We reanalyzed the data of Hsu et al and made the appropriate log transformations by using the graphical data in their Fig 1 (see our Figure). We note the following. First, the mean IgE values from either the normal subjects or the Meniere's patients are not significantly different from those of the other published series; second, the variations in both the normal subjects and the Meniere's patients are far less than those of the other published series.

Although the comparison (*t* test) of the control and Meniere's groups showed no statistical significance, Hsu et al inappropriately attempted to find significance in this analysis by noting that several Meniere's patients had IgE levels higher than controls. Using this method of analysis, we could as readily argue that controls exhibited allergic responses, because the data of Hsu et al also show several Meniere's patients with IgE levels *lower* than those of controls.

Hsu et al then examined the level of circulating immune complexes (CICs) in these Meniere's patients and controls. They state that 42 patients were included in the Meniere's group; however, Fig 2 shows 59 data points. Their discussion of a number of patients more than 2 SD above the mean in the experimental group also ignores the fact that 4 patients in the Meniere's group were more than 2 SD *below* the mean on the line below, and 2 patients were either above or below the 2-SD line in the control group.



Reanalysis of data. Bars show mean ± 2SD.

For reasons that are not clear to us, Hsu et al discard the resolving power inherent in their parametric data (data continuum), convert to nonparametric data (normal and abnormal), conduct a χ^2 test, and show a significant difference between groups. We conducted a parametric analysis of their graphical data (*t* test) and did find a significant difference between Meniere's patients and controls ($df = 100$, $t = 2.64$, $p = .0096$ for a two-tailed test).

A more important consideration in this analysis is: What meaning can we attach to significant differences in absorption measurements of CICs? A slight difference in composition of CICs can greatly alter absorption. Thus, significant differences in absorption can indicate either significant differences in concentration or minor differences in composition. Qualitative analyses of individual CIC components are required. This essential difference is not discussed by Hsu et al.

Next, the authors do attempt to portray such analyses, again inappropriately. They measured immunoglobulin components in CICs and found significant differences. Once again, inappropriate statistical tests were used to analyze the immunoglobulin component data. These data are repeated measures taken from the same subjects. A one-way analysis of variance for repeated measures would be more appropriate. If multiple comparisons with *t* tests are used, the significance levels should be corrected by a Bonferroni test.

An even more disturbing problem is that Hsu et al discarded those data from patients in which IgA, IgG, and IgM levels were below detection threshold. It is not appropriate to discard that part of the data. Those patients having nonmeasurable levels should have been treated as having levels of 0. This enlarges the number of subjects in each group, reduces the means, and increases the variance. Under those circumstances in the IgG group the mean for the Meniere's patients would have been 28.53 and the mean for the control subjects would have been 15.06, with larger SDs than were presented in Table 2. Significance would be questionable. Similarly, in the IgM group, the mean for the Meniere's patients would have been 20.18 and that for the controls 13.69, with larger SDs. It is doubtful whether even a *t* test would have showed significance. The IgA data from all subjects were discarded. Although these IgA levels were below the detection level by this analytic method, this means that the groups do not differ on this measure, supporting the null hypothesis.

In this instance, Hsu et al did not present a graphical display of their raw data, so we cannot reconstruct an appropriate analysis. However, using their number for patients in whom significant levels of IgG and IgM could be detected, we can conduct a nonparametric comparison of the numbers of patients with and without detectable levels of CICs. For IgA, the numbers are not detectable in either group; for IgG, $p = .43$; for IgM, $p = .12$; thus, the number of Meniere's patients in which detectable levels of immunoglobulins could be detected did not differ from that of controls.

The authors present a table (Table 1) that attempts to show a correlation between the degree of hearing loss in Meniere's patients and the number of patients with raised CIC. A true correlation test could have been conducted with these data, but was not. If it had been, age should have been included in a multiple test of correlation. Age-related hearing loss is well known; the extent of Meniere's-related hearing loss is probably related to duration of the disease; and it is likely that immunoglobulin levels show an age-related peak.

In sum, the authors do not present convincing evidence that Meniere's disease is due to either an immediate or a delayed hypersensitivity phenomenon. Misstatements about the number of specimens analyzed and selection of subsets of patients undermine the validity of the paper. Nonparametric statistical tests should not be applied to parametric data.

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To the Editor:

Drs Moss, Kunpittaya, and Sorasuchart (Cervical Necrotizing Fasciitis: An Uncommon Sequela to Dental Infection, *Ann Otol Rhinol Laryngol* 1990;99:643-6) stress correctly the utmost importance of early diagnosis and early extensive surgical removal of all necrotic tissue, combined with the administration of broad-spectrum parenteral antibiotics and intensive care support, in reducing the high mortality rate from necrotizing fasciitis. However, the role of the early commencement of hyperbaric oxygenation (HBO) as an adjunct to the management of necrotizing fasciitis is not mentioned in their article.

Necrotizing soft tissue infection is one of the 12 indications for which HBO has been approved by the Undersea and Hyperbaric Medical Society (UHMS).[1] Hyperbaric oxygenation improves local tissue hypoxia caused by the necrotizing infection and adversely affects anaerobic bacterial growth by direct toxic mechanisms. This bactericidal effect is based on the formation of oxygen free radicals in the absence of free radical–degrading enzymes in the anaerobic bacteria.[2] Restoration of oxygen tissue tension to the area of bacterial invasion is an essential prerequisite for the leukocyte-killing mechanisms of both anaerobic and aerobic pathogens that are oxygen-dependent.[3] Hyperbaric oxygenation also helps to establish a demarcation line between necrotic and viable tissue, thus facilitating more accurate surgical excision with maximal preservation of tissue.[4]

During the last 10 years we have seen 34 patients with necrotizing fasciitis, 5 of whom suffered from head and neck involvement. Our patients were all treated by a uniform rigid protocol consisting of the combination of early surgical debridement, parenteral antibiotics, fluid and electrolyte resuscitation, and HBO. The mean delay between onset of symptoms and operation averaged 25.5 hours. Hyperbaric oxygen was delivered immediately after operation and included breathing 100% oxygen at 3 atmospheres absolute for 90 minutes in a multiplace hyperbaric chamber via a tightly fitting oronasal mask or mechanical ventilation, according to the patient's status. Three HBO sessions were given in the first 24 hours, and two sessions per day thereafter. The most frequent response to HBO was rapid amelioration in clinical and mental status, observed in the majority of our patients at the end of the first HBO session.[5] Three of the patients succumbed to their disease, while 31 recovered, including all 5 patients with head and neck involvement. This mortality rate of 9%, which is much lower than the average 38% reported in the literature,[1] might be attributed at least in part to the relatively short time delay from onset of symptoms to surgical debridement and the inclusion of HBO in our combined treatment protocol.

Avi Shupak, MD
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To the Editor:

Thank you for allowing me to respond to the concerns expressed by Dr Shupak. In the treatment of necrotizing fasciitis, not only are extensive debridement and appropriate antibiotic therapy mandatory, but oxygen treatment also is indispensable. Oxygen treatment alleviates the anaerobic bacterial infection and promotes a demarcation line between dead and living tissue. This line subsequently facilitates the debridement. As oxygen therapy is essential in the treatment of this condition, the idea of using a hyperbaric chamber for a better oxygen-rich atmosphere is deemed empirically correct and effective. Unfortunately, a hyperbaric chamber is not available in our institution. We thank Dr Shupak and accept his idea of using hyperbaric oxygenation in the treatment of anaerobic infection.

Acharee Sorasuchart, MD
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BOOK REVIEWS

Otolaryngic Allergy and Immunology

Helen F. Krause. Hard cover, illustrated, indexed, 318 pages, 1989. WB Saunders, Philadelphia, Pa, $69.

The purpose of this book is to supply a practical overview of head and neck allergy to the student, young physician, and otolaryngic practitioner. It is divided into five sections: 1) clinical immunology, 2) inhalant and epidermal allergy, 3) food allergy, 4) environmental sensitivity, and 5) special management considerations. All sections are logically organized, and all chapters are clearly written and concise.

The section on immunology reviews the basic physiologic mechanisms and reports various alterations in the normal immune state. The clinically pertinent facts are emphasized and detailed as appropriate for this work. Additional and clearer illustrations and captions would be helpful.

Inhalant and epidermal allergy is the second topic discussed. It is a complete review of the topic. There are chapters on the allergic presentation, diagnostic procedures (both in vivo and in vitro), medical management, and immunotherapy. All chapters reflect the clinical thrust of the work and are uniformly readable. The presentation is invaluable as both an instruction and as a review. The information is well illustrated with photographs, diagrams, and charts.

The next section describes the pathophysiology, clinical presentation, diagnosis, and management of food allergy. The concept of fixed and cyclic food allergies is clearly described. The various mechanisms involved in food allergy and the diversity of symptoms elicited are concisely reviewed. The diagnostic and therapeutic modalities are discussed. However, clarification of the strengths and weaknesses of different techniques would be helpful.

Environmental sensitivity is the fourth topic discussed. Its main strength is arousing the reader's clinical suspicion. Diagnostic and therapeutic alternatives are not treated in depth.

A short section touching on allergic emergencies, the aspirin-sensitive patient, and surgery in the allergic patient completes the work. The chapter on management of emergencies is especially pertinent and detailed.

In summary, Dr Krause presents us with an excellent clinical tool overviewing the entire field of otolaryngic allergy. Discussions of clinical immunology and inhalant allergy are especially strong. The work succeeds in its purpose and fills a vacuum that had existed in the literature. As such, it is a valuable addition to the otolaryngic literature.

RICHARD L. NASS, MD
New York, New York

Sensory Systems II: Senses Other Than Vision

Jeremy M. Wolfe. Soft cover, illustrated, 142 pages, 1990. Birkhauser, Boston, Mass, $24.50.

This volume is part of *Readings from the Encyclopedia of Neuroscience*, a series of rather terse summations of diverse topics.

The text houses 65 chapters in a paperback, journal-sized format. Chapters range from four of the five "traditional senses" (excluding vision) to Insect Communication, Bird Navigation, and Sound Localization of the Owl.

Of obvious note in this series is the relegation of "senses" served by our specialty to equivalent status with entomology and zoology. Vision, conversely, commands an entire volume of its own in the *Readings from the Encyclopedia of Neuroscience*. Perhaps this is a bias of the editors. Quite possibly, though, it is a reflection of current research interest in the fields of audition, olfaction, gustation, and vestibular sensation. In this text, hearing receives 7 pages (three chapters), olfaction receives 17 pages (six chapters), taste receives 6 pages (four chapters), and vestibular/proprioceptive sensation receives 21 pages (nine chapters). An additional 2-page chapter on hair cells and a chapter on headache complete that which is obviously germane to our specialty.

Not only are the chapters brief, but so, too, are the references. The references are, in most cases, textbooks, and often dated texts at that. We found some of the chapters interesting reading, but found little to recommend this as a text to true students of the subserved disciplines. For otolaryngologists, we feel that this has rather superficial appeal.

JEFFREY B. BANYAS, MD
DENNIS G. PAPPAS, MD
Birmingham, Alabama

Diagnostic Laryngology: Adults and Children

Bruce N. P. Benjamin. Hard cover, illustrated, indexed, 192 pages, 1990. WB Saunders, Philadelphia, Pa, $95.

Diagnostic Laryngology: Adults and Children is a comprehensive guide to the endoscopic evaluation of the larynx. The book is divided into two sections, with the first a written text with black and white drawings. Clearly written chapters discuss in broad terms the indications for endoscopy, radiographic studies, anesthesia, instrumentation, and endoscopic techniques in adults and children. The chapters on presenting features and indirect laryngoscopy are brief, and the reader would do better by seeking this information elsewhere.

The real strength of the book lies in the second section, which is an excellent endoscopic atlas of the normal and diseased larynx. The color photographs are superb and with the accompanying descriptive paragraphs clearly illustrate each problem. The atlas covers congenital disease, acute inflammatory airway obstruction, foreign bodies, and trauma as well as benign and malignant lesions. Separate chapters cover the nasal cavities and nasopharynx as well as rare and unusual conditions of the larynx. This book provides the endoscopist with a practical atlas for the evaluation of laryngeal pathology.

STEPHEN G. ROTHSTEIN, MD
New York, New York

Microsurgical Tissue Transplantation

D. Riediger and M. Ehrenfeld, editors. Soft cover, illustrated, indexed, 243 pages, 1989. Quintessence Publishing, Chicago, Ill.

This book is based upon contributions of an international symposium of surgeons who met during 1987 to discuss microsurgical tissue transplantation. It is a compilation of their manuscripts presented in soft-cover style. Several are well-organized and comprehensive presentations, but many of the chapters are relatively short and somewhat incomplete as specific topic discussions. The bibliography at the end of each section is adequate. The contributing authors represent an international blend of the established experts in the field of microvascular free tissue transplantation.

The text is divided into four sections consisting of microsurgery of the head and neck region, microsurgery of the oropharyngeal region, microsurgery of the trunk and extremities, and microneural surgery and basic research.

The book represents a compendium of a large amount of important information in a quick review style covering important techniques of microsurgical reconstruction. Residents interested in head and neck reconstruction will find this an interesting source of information.

MARK S. PERSKY, MD
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Hearing: Physiological Acoustics, Neural Coding, and Psychoacoustics

W. Lawrence Gulick, George A. Gescheider, and Robert D. Frisina. Hard cover, illustrated, indexed, 409 pages, 1989. Oxford University Press, New York, NY, $39.95.

The inexorable specialization of many practitioners into the field of otology mandates a basic science review of auditory function. This work provides an excellent review of historical and current research in the fields of hearing and acoustics.

The construction of the book follows a logical progression of the auditory system from source to receptor organ and thence up the auditory pathway to the cerebral cortex. Chapters devoted to the central nervous system are subdivided into certain complex attributes of audition, such as pitch, loudness, localization, and auditory fatigue. Following this thorough review of applicable neuroanatomy and neurophysiology, the final chapter deals rather superficially with pathology and clinical otologic medicine.

We have understood for quite some time the general manner in which sound travels through the ear. This book reviews in detail the original theories of Helmholtz and von Bekesy, together with their contemporary criticisms. This historical chapter provides the reader with the perspective necessary to follow the remainder of the text. In some respects this chapter alone makes the book worthwhile for the aspiring academic otologist.

The authors expertly assimilate work from various disciplines (such as otology, audiology, psychology, histology, and electrophysiology) in order to unravel the mysteries of the inner ear and central auditory systems.

One of the most puzzling problems that is discussed is the perception of pitch. How do we distinguish so accurately among frequencies of sound? To Bekesy's early "traveling wave" theory is added the knowledge of today's histology. As we progress from base to apex along the basilar membrane, the width increases by a factor of 6 and stiffness decreases by a factor of 100. The mass of the organ of Corti increases while density of afferent innervation decreases. The peripheral tuning gradients can therefore account for much of Bekesy's "place" theories, although, as the text indicates, "at a level of precision he could scarcely have imagined." The technology of interferometry has proven this precision.

As we follow the auditory system cranially, we see a preservation of this precision, albeit with greater processing for more complex sounds. Cochlear neurons each have characteristic frequencies and "response areas" to continue the preservation of tonally coded information. Through the ascendance of the auditory pathway, classic research is presented to prove the tonotopic organization of the cochlear nuclei, lateral lemnisci, inferior colliculi, and medial geniculate body of the thalamus. As the signal enters the primary auditory cortex, the text clarifies the differences between the absolute values of frequency and the psychologic perception of pitch. Graphs, in fact, illustrate their nonlinear relationship as psychologic units of pitch (mels) are plotted against frequency in Hertz. The problems of complex tones are reviewed. Often we perceive a pitch corresponding to a frequency completely absent from a complex stimulus. Previous research has shown this to be the case even during masking of the perceived pitch to render the corresponding "place" of the basilar membrane unresponsive. This, as the authors demonstrate, may be due to temporal coding and/or complex wave periodicity. This, of course, adds another element to conventional "place" theories of hearing.

The text treats other auditory phenomena such as timbre, volume, consonance, fatigue, adaptation, and intensity with equal diligence. Discussions of localization and masking follow and provide transition for the abbreviated chapter on hearing loss and clinical audiology.

The authors' highly technical approach, though, often taxes the reader with a tedious style. Although many of the chapters end with a synopsis for clarity, most of the text requires intense study rather than casual perusal.

Both this tedious style and the cursory discussion of pathophysiology and treatment lead us to question the pertinence of this book to the private practitioner. For the practitioner with a consuming interest in otology, however, the comprehensive exposition of normal auditory physiology serves to override these deficiencies. The compilation of knowledge culled from several generations and disciplines should stimulate further research into the field of audition.

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Recent Advances in Clinical Dysarthria

Kathryn M. Yorkston and David R. Beukelman, eds. Soft cover, illustrated, indexed, 276 pages, 1989. College Hill Press, San Diego, Calif, $33.50.

The information contained in this volume was compiled from that presented at the fourth Clinical Dysarthria Conference, held in San Diego, California, in February 1988. The stated purpose of the editors was to make current research findings in the field of dysarthria available to "clinically active" speech/language pathologists and graduate students.

The text is divided into five sections: Assessment Procedures, Clinical Management Techniques and Procedures, Difficult Cases, Parkinson's Disease, and Spasmodic Dysphonia. Illustrations and figures help the reader to comprehend the highly technical data and detailed case reports presented. The text is accompanied by a comprehensive, well-organized index. Since the book is a valuable reference source, a hardbound edition would perhaps be more practical than the softbound volume.

The clinician who has access to specialized equipment and techniques such as personal microcomputers, fluoroscopy, and electromyography will find this book very useful. The authors of one chapter were thoughtful enough to include an appendix from which the sources of the special equipment used in their research may be obtained.

For students or clinicians who rely on "traditional" management techniques, this text is an excellent source of information that may help in making management decisions, including when to seek outside assistance. The volume would also be of use to physicians interested in the most recent assessment and treatment techniques for their dysarthric patients.

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Multiple-choice Questions in Otolaryngology With Explanatory Answers

Ramindar S. Dhillon and James W. Fairley. Soft cover, 217 pages, 1989. The MacMillan Press, London, England.

Multiple-choice Questions in Otolaryngology is designed as a review of current otolaryngology topics for residents in training. The book contains 1,590 questions subdivided into 318 main subjects with five independent true/false statements. The questions appear on the left-hand page, and the answers with brief explanations on the right. The questions are further subdivided into sections covering the major areas in otolaryngology (ear; nose and sinuses; larynx and tracheobronchial tree; mouth; pharynx and esophagus; and general subjects).

The book is not intended to be used in place of standard textbooks, but rather as a quick and easy method to review and pinpoint topics that require more study. The questions test current information, and the authors have included short notes with the answers in an attempt to clarify the responses. The book provides an active forum for reviewing and testing knowledge of otolaryngology and should be suggested as a complement to standard textbooks.

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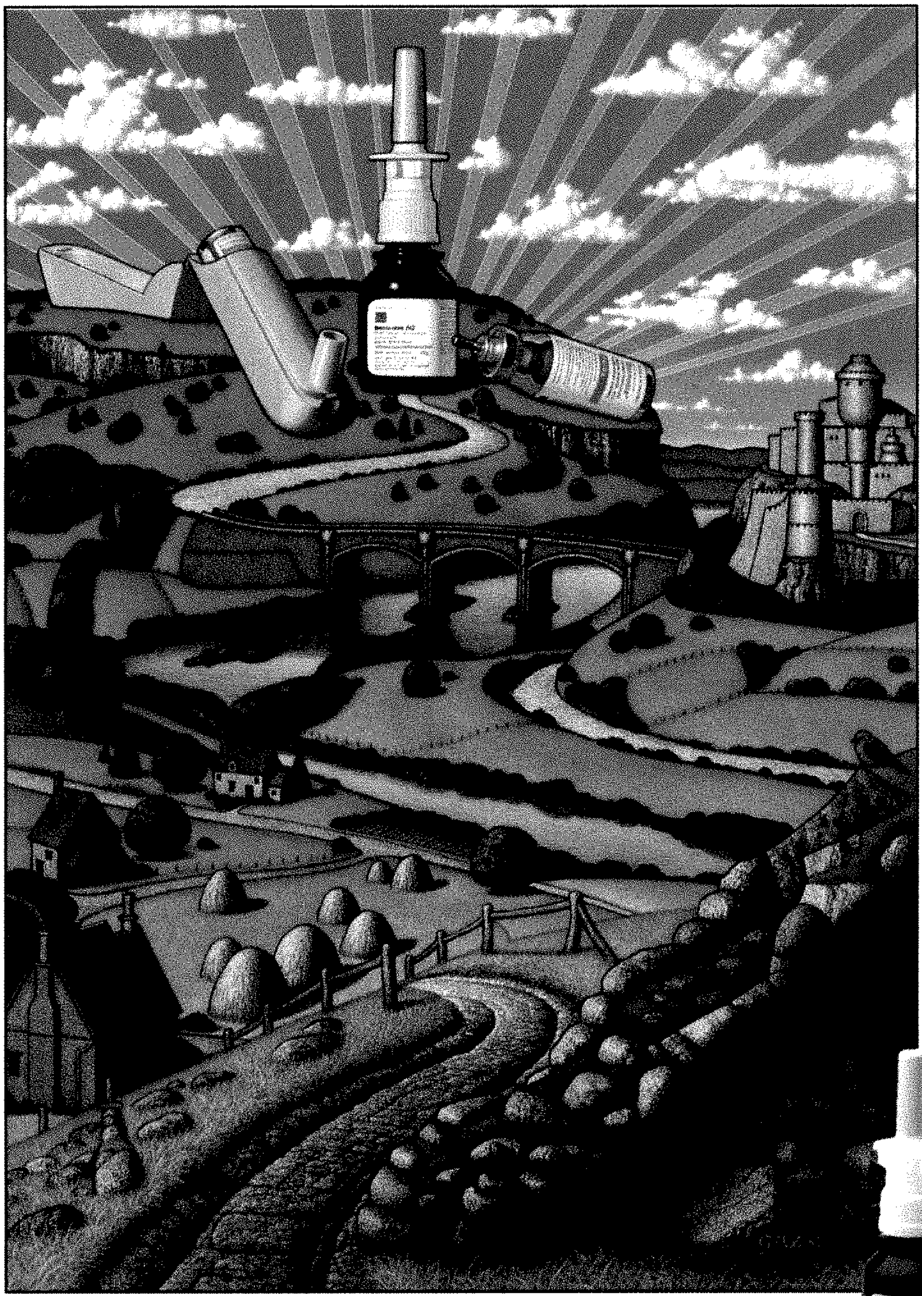

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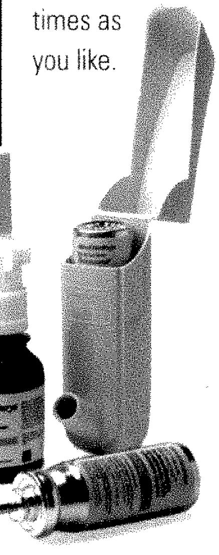

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The ANNALS is available in microform from University Microfilms, International, 300 North Zeeb Road, Ann Arbor, MI 48106.

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY (ISSN 0003-4894) is published monthly by Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108. Second-class postage paid at St Louis, Mo. POSTMASTER: Send address changes to Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108.

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ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY
ANNALS OF HEAD & NECK MEDICINE & SURGERY®

VOLUME 100 JUNE 1991 NUMBER 6

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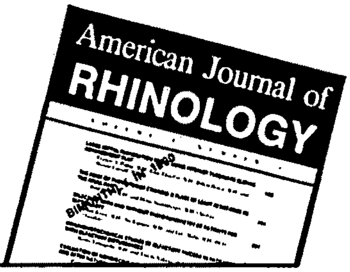

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PRIMARY TRACHEOJEJUNAL SHUNT OPERATION FOR VOICE RESTORATION FOLLOWING PHARYNGOLARYNGOESOPHAGECTOMY

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A primary tracheojejunal shunt operation was performed for voice restoration following pharyngolaryngoesophagectomy with free jejunum reconstruction for advanced hypopharyngeal cancer. A fistula was created between the membranous part of the trachea and the lower part of the transplanted jejunum. The membranous part of the trachea was tubed to construct the tracheojejunal shunt. All three patients who had the tracheojejunal shunt operation retained phonatory function. Pitch formation was seen in the voice waveform with use of the tracheojejunal shunt. No leakage was seen at all during deglutition and a swallowing function was obtained in all patients who had the tracheojejunal shunt.

KEY WORDS — advanced hypopharyngeal cancer, free jejunum reconstruction, pharyngolaryngoesophagectomy, tracheojejunal shunt, voice restoration.

INTRODUCTION

During the past 12 years we have been performing the tracheoesophageal (TE) shunt operation for the purpose of voice restoration following total laryngectomy.[1,2] The purpose of this technique is to divert the exhaled air through the TE shunt into the esophagus, where the vibration occurs and sound is produced. The speech obtained following the TE shunt operation was satisfactory even when compared with that of normal subjects.[3,4]

On the basis of successful results of postlaryngectomy speech with the TE shunt operation, the primary tracheojejunal (TJ) shunt operation was performed for the said purpose following pharyngolaryngoesophagectomy with free jejunum reconstruction for advanced hypopharyngeal cancer.

SUBJECTS AND METHODS

Subjects. Three patients with hypopharyngeal cancer underwent the primary TJ shunt operation. The summary data of the patients are seen in Table 1, showing the TNM classification, age at operation, sex, the length of jejunum used, first day of phonation, the duration of a sustained vowel, and the length of time TJ speech had been used. All patients had a pharyngolaryngoesophagectomy with bilateral neck dissection. One received preoperative radiotherapy of 40 Gy.

Surgical Procedure. After the pharyngolaryngoesophagectomy with bilateral neck dissection, a 10- to 14-cm segment of proximal jejunum is removed with its vascular arcade. The bowel and abdomen are closed in the usual fashion. The jejunal artery is anastomosed to the transverse cervical artery and the jejunal vein is anastomosed to the external jugular vein. The ischemic time of jejunal grafts during transplantation is 2 hours.

The membranous part of the trachea (tracheal flap) measuring 2 cm in width and 2 cm in length is used as an inferiorly based flap for construction of the TJ shunt. After the lower half of the tracheostoma is formed, the pharyngeal stump and oral side of the jejunum are anastomosed and the posterior half of the esophageal stump and proximal side of the jejunum are approximated (see Figure, A).

An 8-mm midline vertical incision is made starting just below the superior margin of the tracheal flap, and a vertical incision of free jejunum corresponding to that of the tracheal flap is carried out to

TABLE 1. SUMMARY DATA OF PATIENTS

Case	*Age (yr)*	*Sex*	*Tumor Site*	*TNM*	*Length of Jejunum (cm)*	*Initial Phonation (d)*	*Duration of Sustained Vowel (s)*	*Use of Tracheojejunal Speech (mo)*
1	57	F	Posterior wall	T4N1M0	12	19	10	13
2*	73	F	Posterior wall	T4N0M0	10	51	12	12
3	63	M	Pyriform sinus	T3N0M0	14	30	8	10

TNM — tumor, node, metastasis.

*Preoperative irradiation.

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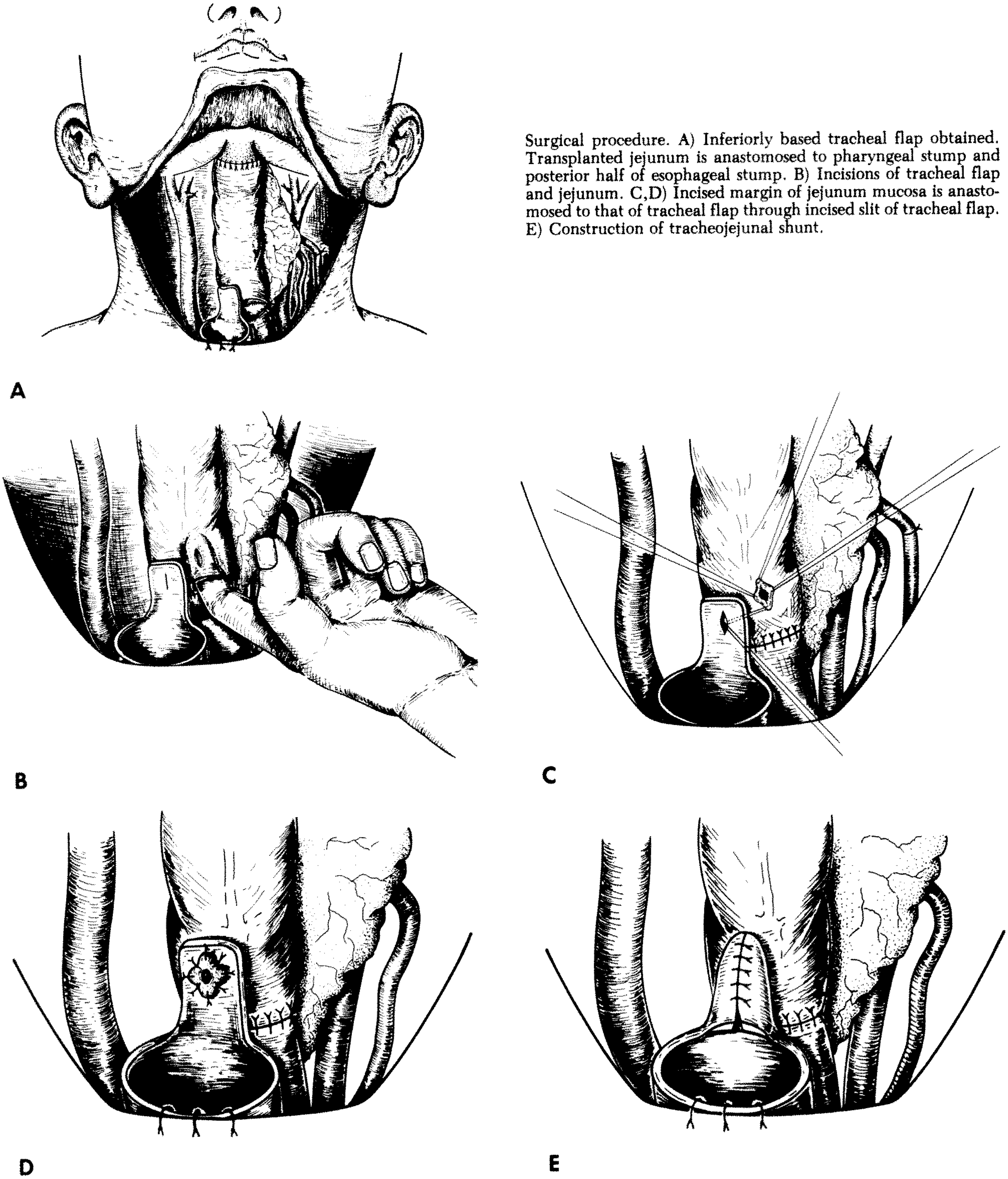

Surgical procedure. A) Inferiorly based tracheal flap obtained. Transplanted jejunum is anastomosed to pharyngeal stump and posterior half of esophageal stump. B) Incisions of tracheal flap and jejunum. C,D) Incised margin of jejunum mucosa is anastomosed to that of tracheal flap through incised slit of tracheal flap. E) Construction of tracheojejunal shunt.

enter the jejunal lumen (see Figure, B).

After the anterior half of the anastomosis of the esophagojejunal junction is completed, the incised margin of the jejunal mucosa is anastomosed to that of the tracheal flap through the incised slit of the tracheal flap (see Figure; C,D). The TJ fistula is located 2 cm away from the esophagojejunal junction. The tracheal flap is tubed to construct the TJ shunt (see Figure, E).

Voice can be produced by occluding the tracheostoma with a finger to divert the exhaled air through the TJ shunt into the jejunum, where the sound is produced.

Phonatory Function Analysis. The intensity and fundamental frequency of the voice and airflow

TABLE 2. PHONATORY FUNCTION

Case	*Mean Period (ms)*	*Fundamental Frequency (Hz)*	*Intensity (dB SPL)*	*Airflow Rate (mL/s)*
1	3.1, 10.0	100, 323	68-76	20- 50
2	2.5, 12.8	78, 400	72-80	30- 50
3	3.0, 10.3	97, 333	75-85	50-100

SPL — sound pressure level.

rate during phonation were measured by a phonatory function analyzer (PS-77, Nagashima Co) consisting of a microphone, a hot-wire flowmeter, and a three-channel pen recorder. The fundamental frequency was derived from the flowmeter through the filter system. The intensity of voice was measured by a microphone placed 25 cm from the flowmeter. Airflow rates were measured by a hot-wire flowmeter. Each subject was asked to phonate in a comfortable fashion.

A voice waveform was observed on the display as an electronic signal. A series of sustained vowels from each subject were recorded on an audiotape. Recording was done in a soundproof room with use of a high-quality tape recorder–microphone system. Subjects were requested to sustain the vowel /a/ in as steady a manner as possible at a conversational level of loudness. The output from the tape recorder was displayed serially on a graphic terminal (Signal Processor 7T17). The waveforms of a 1-second segment were analyzed for period-by-period measurement. The computer program provided the duration for each cycle, with a resolution of 0.05 milliseconds. The mean period and mean fundamental frequency were obtained by calculating the average of these cycle-to-cycle measurements.

RESULTS

All patients acquired voice capability with the TJ shunt and consistently use TJ shunt speech. Initial phonation was obtained on the 33rd postoperative day, on average. The duration of sustained vowels ranged from 8 seconds to 12 seconds (Table 1).

The voice intensity ranged from 68 dB sound pressure level (SPL) to 85 dB SPL, and the airflow rate during phonation ranged from 20 mL/s to 100 mL/s. The fundamental voice frequency could not be detected by the phonatory function analyzer because of the noisy component of the voice (Table 2).

Observation of the voice waveform revealed pitch formation. Both regular and noisy components were found in the voice waveform during phonation in each subject. The regular component of the voice waveform had two different values of mean fundamental frequency — that is, about 100 Hz and above 300 Hz, respectively (Table 2).

As far as the swallowing function is concerned, all patients could swallow solid foods and liquids, and natural peristalsis was seen on radiographic examination. The patients could swallow more satisfactorily than the patients reconstructed with other grafts such as the pectoralis major myocutaneous flap and the radial forearm free flap. No spasm, regurgitation, or aspiration was seen at all.

DISCUSSION

Free skin grafts, cervical skin flaps, tubed deltopectoral flaps, myocutaneous flaps, and visceral transposition have been employed for reconstruction of digestive continuity after pharyngolaryngoesophagectomy.[5-13]

Immediate jejunal autograft was proposed for reconstruction of the defect of the hypopharynx and cervical esophagus with use of a microvascular technique in 1959.[14] Since then various free grafts of abdominal viscera, including the small colon, gastric antrum, and sigmoid colon, have been used to restore digestive continuity.[15-17]

The recent advent of microvascular surgery has provided more alternatives for reconstructing defects of the pharyngoesophagus.[18,19] Jejunal autotransplantation with microvascular reanastomoses is now recognized as one of the most reliable methods of restoring digestive continuity. The advantage of this technique is a one-stage reconstruction without cicatricial stricture.

Although many authors have reported successful results of reconstruction of the cervical esophagus and hypopharynx with a variety of grafts and flaps following pharyngolaryngoesophagectomy, few attempts at voice restoration have been found in the literature. Saito et al[20] reported a tracheogastric shunt method using the gastric mucosal tube for voice restoration with the gastric pull-up reconstruction following pharyngolaryngoesophagectomy. This shunt requires a stent, and the shunt's downward direction is its disadvantage in introducing expiratory air into the oral cavity. Ehrenberger et al[21] proposed a siphonlike tracheohypopharyngeal shunt using the free jejunum.

All three patients who had the TJ shunt operation retained phonatory function. Voice quality of the TJ shunt speakers was noisy compared to that of the TE shunt speakers. Mean values of sustained vowel duration of the TE and TJ shunt speakers were 17.3 seconds and 10.0 seconds, respectively. The value of voice intensity with the TJ shunt speakers ranged from 66 dB SPL to 85 dB SPL, while that of the TE shunt speakers ranged from 65 dB SPL to 95 dB SPL. Although the airflow rate of the TJ shunt speakers was below 100 mL/s, that of the TE shunt speakers ranged from 50 mL/s to 300 mL/s. The differences of phonatory function between the TJ shunt and TE shunt may be affected by many factors — for example, the period of speech, the fold of the vibratory source, and natural peristalsis. Pitch formation was seen in the voice waveform with the TJ shunt as well as with the TE shunt. Although each of the TE shunt speakers had only one value of mean fundamental frequency, ranging from 30 to 200 Hz, each of the TJ shunt speakers had two different values of mean fundamental frequency — that is, 100 Hz and above 300 Hz. The natural peristalsis of the jejunum may influence production of the high fundamental frequency during phonation.

Although a surgical attempt to avoid aspiration is advisable in the TE shunt operation,[22] no leakage from the TJ shunt was seen at all, regardless of the simple fistulization between the trachea and the jejunum. The tracheal flap, Kerckring's fold, and the intestinal villi of the transplanted jejunum may prevent aspiration.

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Ann Otol Rhinol Laryngol 100:1991

INSERTION OF THE TENSOR VELI PALATINI MUSCLE INTO THE EUSTACHIAN TUBE CARTILAGE IN CLEFT PALATE CASES

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Differences in insertion of the tensor veli palatini muscle (TVPM) into the lateral lamina of the eustachian tube (ET) cartilage between cleft palate (CP) cases and controls were investigated histologically. Thirty temporal bones with entire ETs were studied: 10 from individuals with CP and 20 controls. The ratio of the length of the ET cartilage with insertion of the TVPM to its total length from the nasopharyngeal end to near the tubal isthmus was calculated in all 30 cases. In all 20 controls, but in only 6 of 10 CP cases, the TVPM inserted into the lateral lamina of the ET cartilage at its tip portion (χ^2 test, $p<.025$). The ratio was significantly smaller in CP cases (0.178 ± 0.172) than in controls (0.419 ± 0.120) ($t=4.305$, $p<.001$). We believe that abnormal insertion of the TVPM into the ET cartilage is one of the causes of the functional obstruction of the ET that contributes to the frequent bouts of otitis media experienced by those with cleft palate.

KEY WORDS — cleft palate, eustachian tube cartilage, muscle insertion, otitis media, tensor veli palatini muscle.

INTRODUCTION

Recently, function and dysfunction of the eustachian tube (ET) and its accessory structures have been recognized as important factors in the causation of middle ear diseases.[1-3] In fact, Bluestone et al[4,5] found that all of 116 infants less than 2 years old with cleft palate (CP) were found to have otoscopic evidence of middle ear disease. In another study,[6] of 250 CP patients of all ages, 42.4% were found to suffer from middle ear diseases.

The study reported upon in this paper was conducted to investigate the connection between frequent occurrence of otitis media and anomalies of the ET accessory structures in individuals with CP. Specifically, insertion of the tensor veli palatini muscle (TVPM), which has been shown to be the muscle that dilates the tubal lumen,[7-9] was studied.

MATERIALS AND METHODS

Thirty temporal bone specimens that included the entire ET and its accessory structures were examined. Ten specimens were from children with CP (32 gestational weeks to 3 years old); and 20 specimens from children without malformation (33 gestational weeks to 2 years old) served as controls. All specimens were processed histologically according to the technique described by Sando et al[10] for light microscopic study. Serial 30-μm-thick histologic sections were cut vertically in the plane perpendicular to the long axis of the ET. Every 20th section was stained with hematoxylin and eosin and evaluated under a light microscope.

Insertion of the TVPM into the tubal cartilage was defined as incorporation of the tendon of the TVPM into the perichondrium of the tip of the lateral lamina of the tubal cartilage. This was evaluated in serial histologic sections of all 30 specimens. The length of the insertion (the distance along the long axis of the ET cartilage where the tendon of the TVPM inserted into the cartilage) was calculated from the number of histology sections in which the tendon was seen to insert and the thickness of the sections. The ratio of this length to the total length of the ET cartilage from nasopharyngeal end to isthmus portion was defined as the insertion ratio (Fig 1).

Otitis media, represented by inflammation of the mucosa of the promontory,[11] was graded as follows (Fig 2): grade 1, minimal or no submucosal infiltration of mononuclear round cells; grade 2, moderate

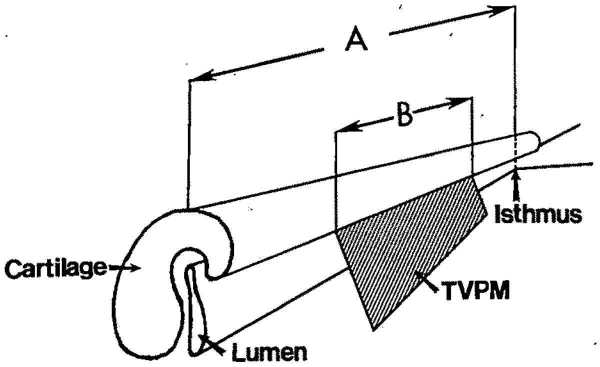

Fig 1. Schematic representation of "insertion ratio," which is length of eustachian tube cartilage involved by insertion of tensor veli palatini muscle (TVPM; B) divided by total length of eustachian tube from nasopharyngeal orifice to isthmus portion (A).

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Supported by National Institutes of Health research grant NS 16337.

Presented at the AAO-HNS/ARO Research Forum during the 93rd annual meeting of the American Academy of Otolaryngology–Head and Neck Surgery Foundation, New Orleans, Louisiana, September 24-28, 1989.

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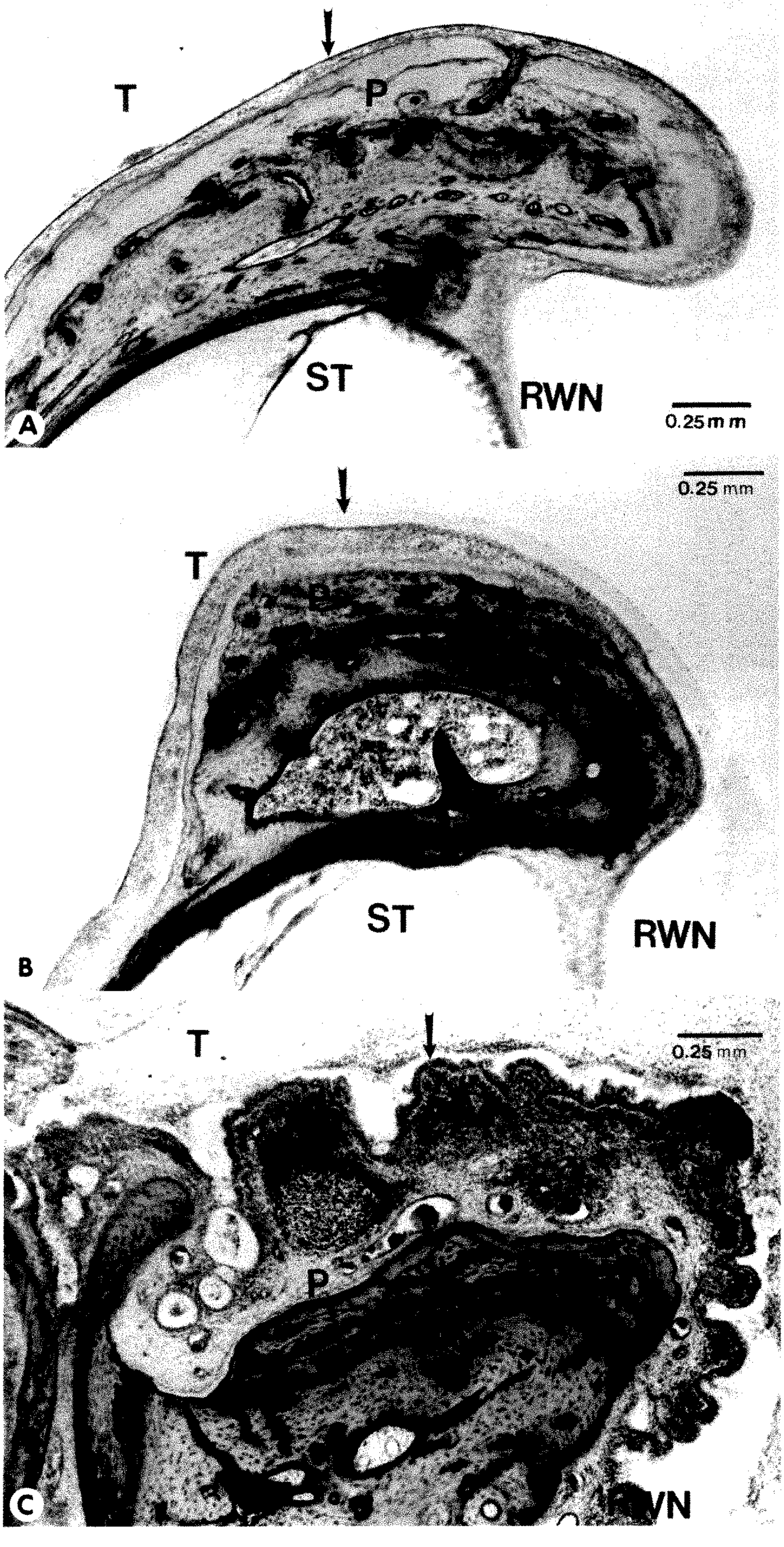

Fig 2. Histologic sections (H & E) showing A) grade 1, B) grade 2, and C) grade 3 inflammation (arrows). P — promontory, RWN — round window niche, ST — scala tympani, T — tympanic cavity.

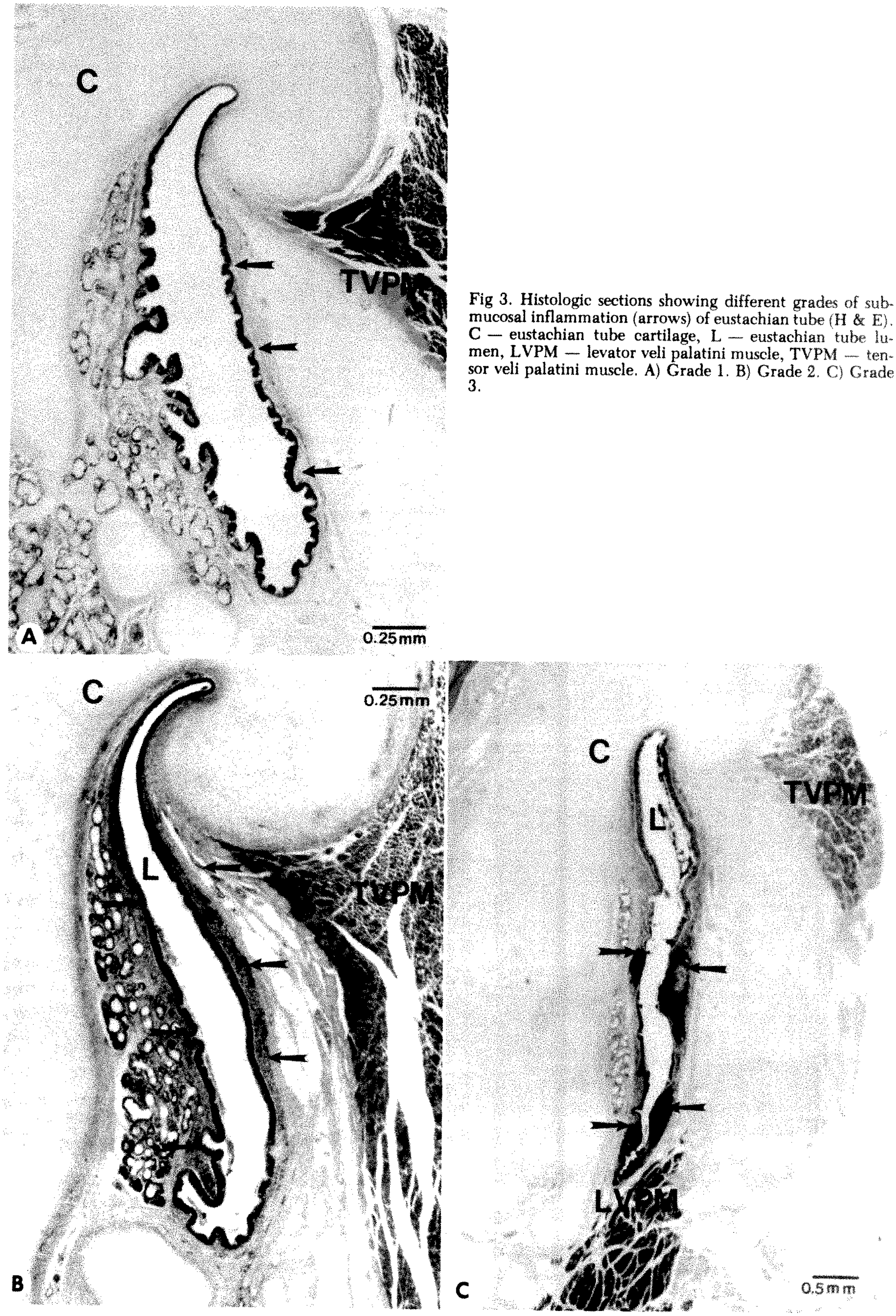

Fig 3. Histologic sections showing different grades of submucosal inflammation (arrows) of eustachian tube (H & E). C — eustachian tube cartilage, L — eustachian tube lumen, LVPM — levator veli palatini muscle, TVPM — tensor veli palatini muscle. A) Grade 1. B) Grade 2. C) Grade 3.

submucosal infiltration of mononuclear round cells without any significant mucosal metaplasia; grade 3, severe submucosal infiltration of mononuclear round cells with significant mucosal metaplasia.

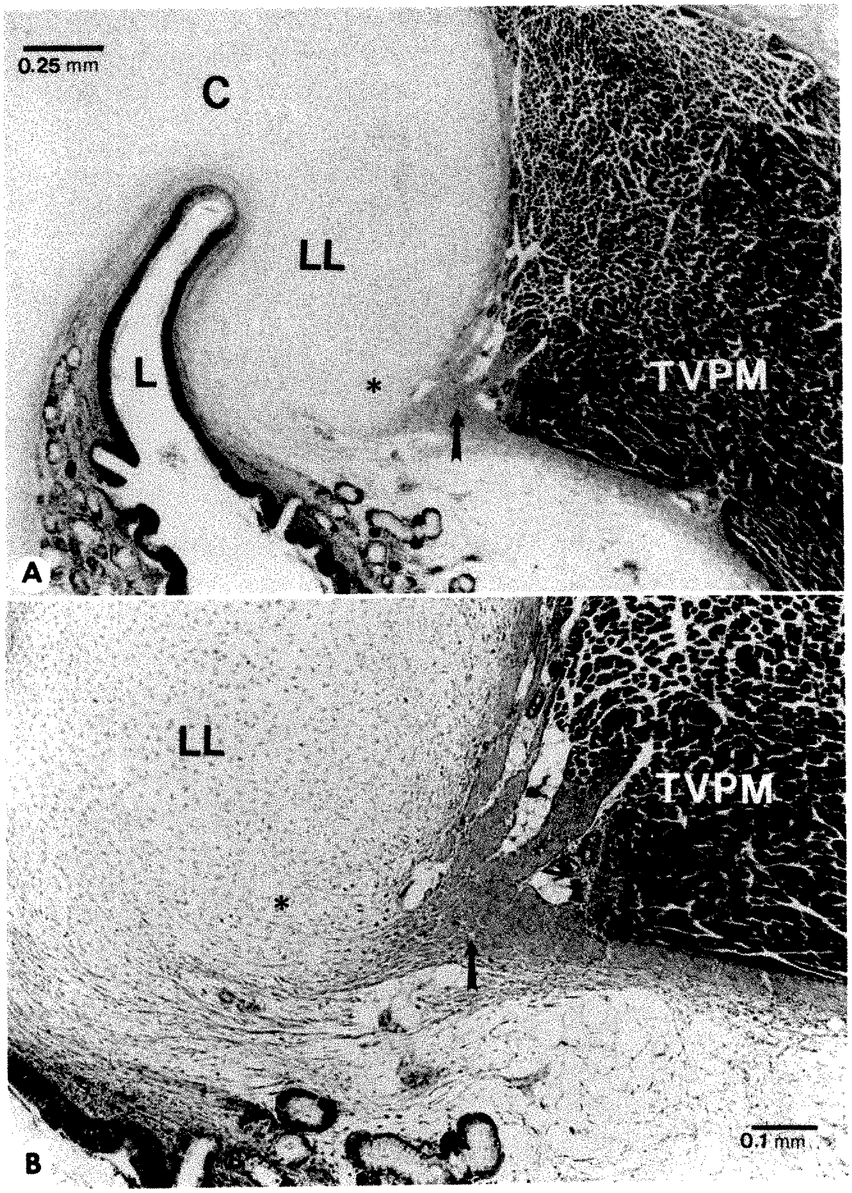

Fig 4. Histologic section showing normal insertion (arrows) of tensor veli palatini muscle (TVPM) tendon into tip portion (*) of lateral lamina (LL) of eustachian tube cartilage (C) from 1-month-old boy (H & E). A) Low-power view of tip. L — lumen. B) Enlarged view of tip.

The degree of inflammation in the mucosa of the ET was also examined in the midcartilaginous portion of the ET and graded as follows (Fig 3): grade 1, minimal or no submucosal infiltration of mononuclear round cells; grade 2, moderate submucosal infiltration of mononuclear round cells; grade 3, severe submucosal infiltration of mononuclear round cells forming lymphoid tissue.

RESULTS

Insertion of TVPM Into Lateral Lamina of Tubal Cartilage. In all 20 controls, the TVPM inserted into the tip of the lateral lamina of the ET cartilage (Fig 4). However, in 4 of 10 CP cases there was no insertion of the TVPM into the lateral lamina anywhere along the cartilage (Fig 5). In the remaining 6 CP cases, although some insertion was observed, fewer tendon and muscle fibers were noted than in controls (Fig 6). In all CP cases, adipose or fibrous connective tissue seemed to interrupt insertion of the tendon of the TVPM into the lateral lamina. The difference in incidence of TVPM insertion between the CP cases and controls was significant (χ^2 test, $p<.025$).

Insertion Ratio. The average insertion ratio (Fig 7) was 0.419 ± 0.120 for 20 controls, but only 0.178 ± 0.172 for 10 CP cases. There was a significant difference in the insertion ratio between these two groups ($t = 4.305$, $p<.001$). Moreover, even if the 4 CP cases with no insertion of the TVPM are excluded from calculation, the average for 6 CP cases is only 0.297 ± 0.118 — still significantly less than for controls ($t = 2.106$, $p<.05$).

Inflammatory Findings in Middle Ear. Of the CP cases with no insertion of the TVPM, only 1 case (25%) showed grade 1 inflammation in the middle ear (Table 1). Two cases and 1 case, respectively,

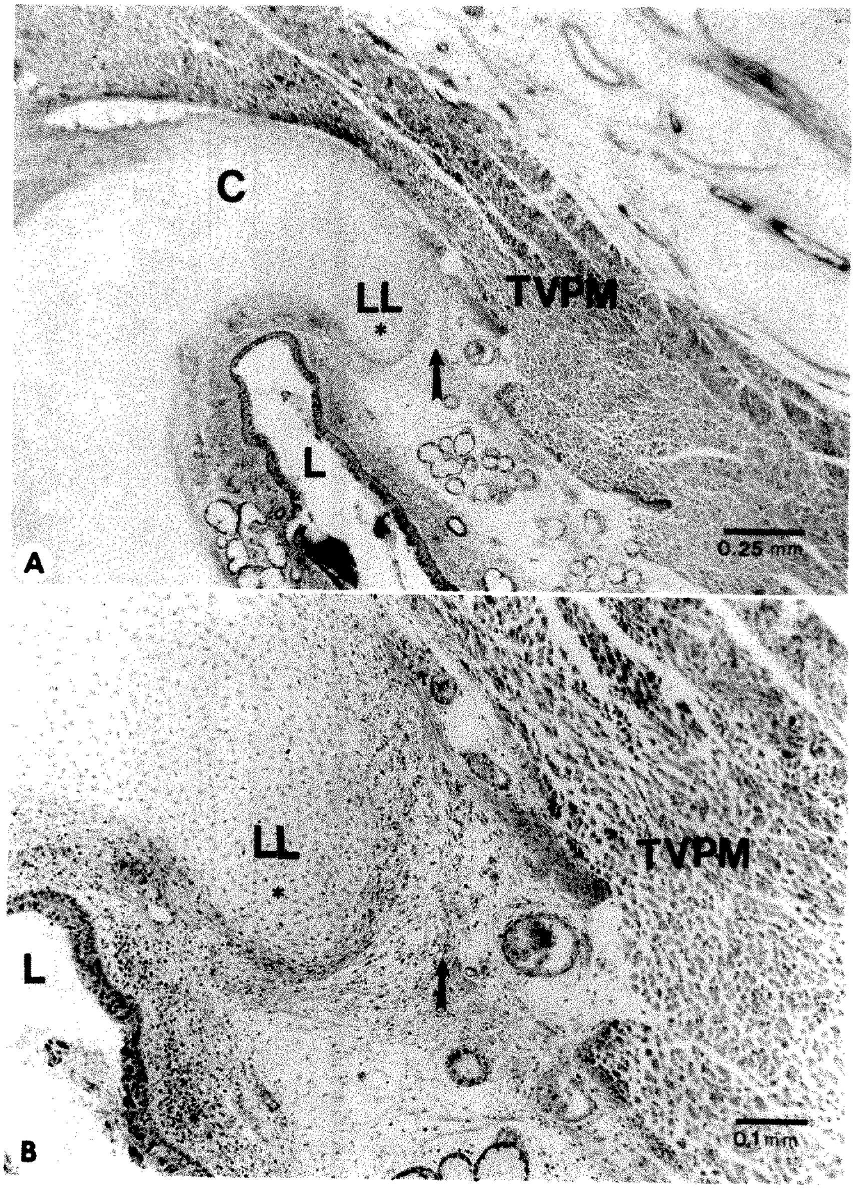

Fig 5. Histologic section from 6-week-old girl with cleft palate showing site (arrows) in which insertion of tensor veli palatini muscle (TVPM) into tip portion (*) should have occurred but is lacking (H & E). C — cartilage, L — lumen, LL — lateral lamina. A) Low-power view of tip. B) Enlarged view of tip.

had grade 2 and grade 3 inflammation. Of the remaining 6 CP cases with poor insertion of the TVPM, grade 1 inflammation was present in 3 cases (50%), grade 2 in 1, and grade 3 in 2. Of the 20 controls, 15 (75%) showed grade 1 inflammation in the middle ear. Grade 2 and grade 3 were present in 5 and no cases, respectively.

In specimens from children older than 1 month, the single CP case (100%) with no insertion of the TVPM showed grade 3 inflammation, 1 of 3 (33%) CP cases with poor insertion of the TVPM showed grade 2 inflammation, and 2 of 3 cases (67%) showed grade 3 inflammation. On the other hand, for 8 controls, 5 (62.5%), 3 (37.5%), and no cases (0%), respectively, showed grades 1, 2, and 3.

Inflammatory Findings in Eustachian Tube. Of the 4 CP cases with no insertion of the TVPM into the ET cartilage, 3 cases showed grade 1 inflammation in the ET, whereas the remaining case showed grade 2 inflammation; no case had grade 3 inflammation (Table 2). In the 6 CP cases with poor insertion of the TVPM, grade 1 inflammation was present in 3 cases, while grade 2 and grade 3 were present in 1 and 2 cases, respectively. Of the 20 controls, 15 cases showed grade 1 inflammation in the ET. Grades 2 and 3 were present in 4 and 1 cases, respectively.

Of note is that among specimens from children older than 1 month, 2 (50%) of 4 CP cases with no or poor insertion of the TVPM showed grade 3 inflammation, and the remaining 2 (50%) showed grade 2 inflammation; on the other hand, in 8 controls, 3 (37.5%) and 4 (50%), showed grades 1 and 2, respectively, whereas only 1 case (12.5%) showed grade 3 inflammation.

In the CP case (36 gestational weeks old) with no insertion of the TVPM, the epithelial lining of the ET was disrupted and the ET lumen was almost

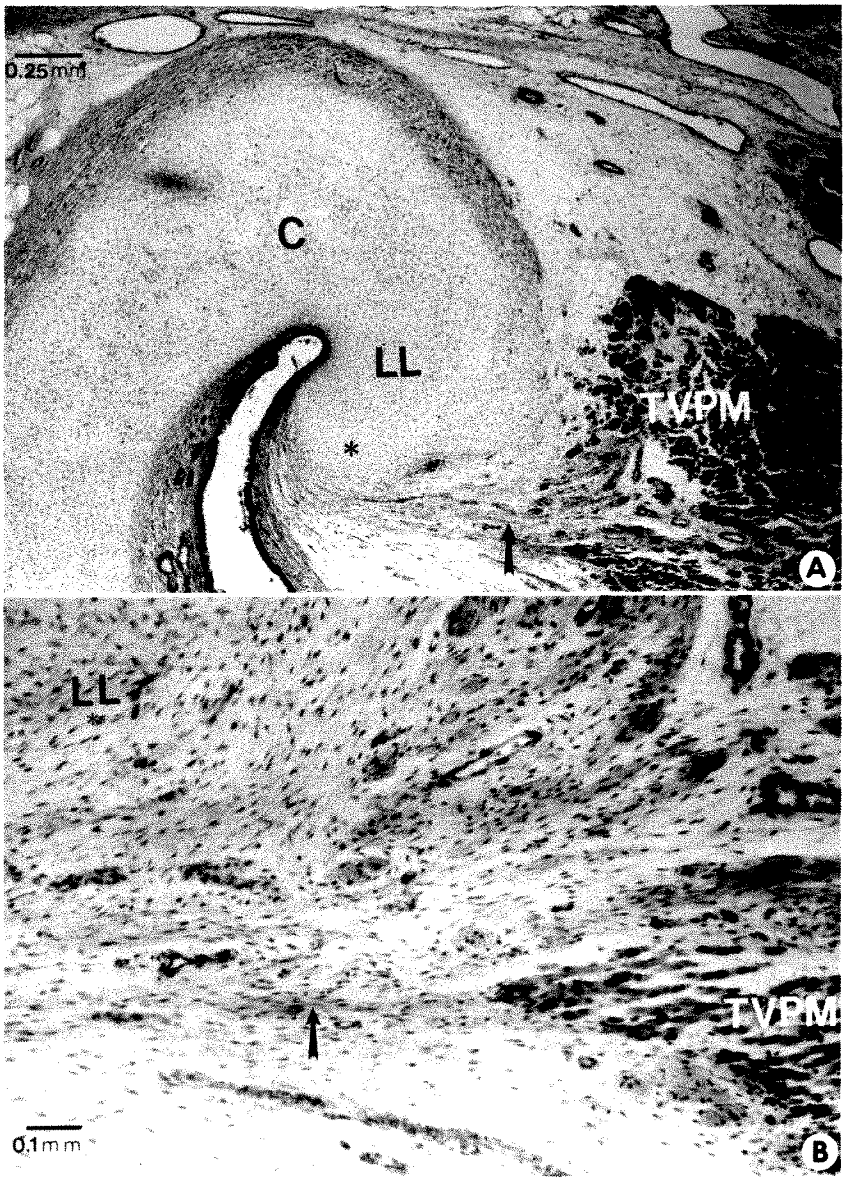

Fig 6. Histologic section from 1-day-old boy with cleft palate showing poor insertion (arrows) of tensor veli palatini muscle (TVPM) into tip portion (*) of lateral lamina (LL) of eustachian tube cartilage (C) (H & E). A) Low-power view of tip. B) Enlarged view of tip.

collapsed by connective tissue; only the superior portion was opened (Fig 8). This case, which had grade 1 inflammation in the middle ear, showed grade 2 inflammation in the ET. In the other 29 cases, there was no mechanical or organic obstruction of the ET lumen.

DISCUSSION

To date, two basic theories have been proposed for the mechanism by which the tubal lumen is dilated. One theory postulates that the tubal cartilage is essentially fixed to the cranial base and that dilation of the ET lumen occurs by contraction of the TVPM, which inserts into the lateral membranous wall of the ET as reported by Rood and Doyle.[12] The other theory postulates that the tube rotates by cooperative contraction of the TVPM and levator veli palatini muscle (LVPM); this theory was proposed by Proctor.[13] For either of these mechanisms, effective contraction of the TVPM is necessary to dilate the tubal lumen effectively.

Abnormal course and insertion of the LVPM[1,14] and hypoplasia of the TVPM[15] have been discussed as possible mechanisms of dysfunction in tubal dilation. Abnormal course and insertion of the TVPM have also been cited as possible causes of dysfunction in fetuses with CP.[16] The present study adds further support to the hypothesis that the anatomic abnormalities of the TVPM affect ET function, at least in CP cases.

In as many as 4 of 10 CP cases in this study, the TVPM failed to insert anywhere on the tip of the lateral lamina. Even in the remaining 6 CP cases with some insertion, the insertion seemed weaker than in controls. Such poor insertion of the TVPM may lead to ineffective transmission of force laterally or inferiorly or both to the lateral lamina, and

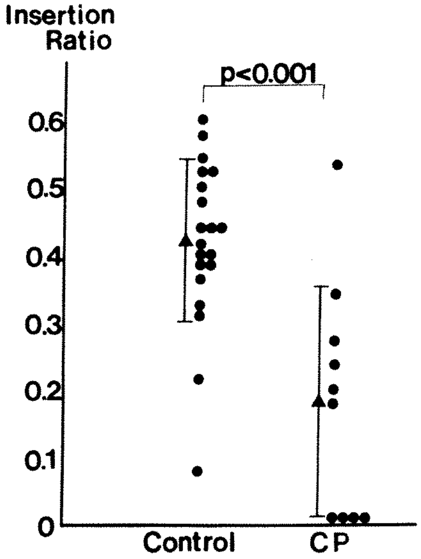

Fig 7. Insertion ratio in cleft palate (CP) cases compared to insertion ratio in control cases.

thus achieve insufficient dilation of the tubal lumen, particularly in its superior portion.

Six of the 10 CP cases used in this study also involved other anomalies of the cranium that could have affected the insertional anatomy of the TVPM and/or the auditory tube. The insertion ratios of these 6 cases, however, did not show a specific tendency different from the overall group. Therefore, the poor insertion of the TVPM to the tip portion of the lateral lamina of the tubal cartilage in CP cases is considered to be characteristic of CP.

Several causes for the high incidence of otitis media in individuals with CP have been suggested: contamination of the velopharyngeal portion by paranasal sinusitis,[17] abnormality of such palatal muscles as the LVPM[1,14] and TVPM,[15,16] and congenital anomalies of the tubal cartilage.[18] Abnormality of the palatal muscles is assumed to promote otitis media by decreasing the ability to dilate the tubal lumen, thus preventing equalization of middle ear pressures. This mechanism of ET dysfunction in an infant with CP was termed "functional obstruction" by Bluestone.[4] Recently, Honjo[6] reported that during observation under flexible endoscopy, the pharyngeal orifice of the ET opened in only 58.5% of CP patients during swallowing and in only 25.8% during mouth opening; Honjo[6] also reported that the incidence of middle ear disease was higher in the CP patients whose ETs did not open during those behaviors than in those whose ETs opened.

We found that children with CP with no or poor TVPM insertion tended to have severe inflammation in the middle ear. This tendency was even stronger in children older than 1 month — probably because otitis media is basically an acquired disease and is very rarely present just after birth, even in CP cases. Moreover, in most of these cases no substance obstructed the ET lumen. Accordingly, "functional obstruction" caused by an anomaly of TVPM insertion, rather than "mechanical obstruction" of the ET lumen, is considered to be the factor most likely promoting otitis media.

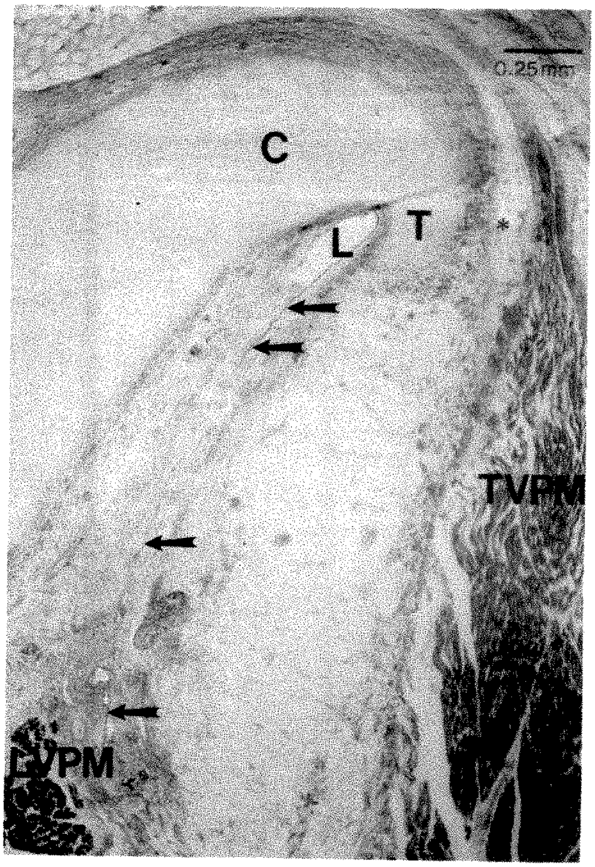

Fig 8. Histologic section from 36-gestational-weeks' girl with cleft palate showing no insertion of tensor veli palatini muscle (TVPM; *) into tip portion (T) of lateral lamina of eustachian tube cartilage (C) (H & E). Also shown is eustachian tube lumen, collapsed, except in its superior portion (L), by surrounding connective tissue. Note that epithelial lining (arrows) of eustachian tube is obstructed. LVPM — levator veli palatini muscle.

Of 10 CP cases, 1 case (a 36-gestational-weeks' girl who lived only 3 days after birth and had grade 1 inflammation in the middle ear) had severe stenosis of the ET lumen as well as no insertion of the TVPM into the tip of the lateral lamina of the ET cartilage. The stenosed area had a trace of disrupted epithelium and a collapsed ET lumen, with

TABLE 1. CORRELATION BETWEEN TVPM INSERTION AND GRADE OF MIDDLE EAR INFLAMMATION

	Grade 1	*Grade 2*	*Grade 3*	*Total*
CP cases				
No insertion	1 (0)	2 (0)	1 (1)	4 (1)
Poor insertion	3 (0)	1 (1)	2 (2)	6 (3)
Control cases	15 (5)	5 (3)	0 (0)	20 (8)

Numbers in parentheses are numbers of specimens from children older than 1 month.

TVPM — tensor veli palatini muscle, CP — cleft palate.

TABLE 2. CORRELATION BETWEEN TVPM INSERTION AND GRADE OF ET INFLAMMATION

	Grade 1	*Grade 2*	*Grade 3*	*Total*
CP cases				
No insertion	3 (0)	1 (1)	0 (0)	4 (1)
Poor insertion	3 (0)	1 (1)	2 (2)	6 (3)
Control cases	15 (3)	4 (4)	1 (1)	20 (8)

Numbers in parentheses are numbers of specimens from children older than 1 month.

TVPM — tensor veli palatini muscle, ET — eustachian tube, CP — cleft palate.

no mononuclear round cell infiltration. We believe this child had a well-developed tubal lumen that later became mostly obstructed because of an unknown factor. We also believe that had she lived longer, this infant's middle ear inflammation might have been more severe as a result of both functional and mechanical obstruction. It is interesting to note that similar findings in the ET lumen have been reported in one Down syndrome case.[19]

In conclusion, this study suggests that no or poor insertion of the TVPM into the ET cartilage is one of the causes of the "functional ET obstruction" in CP cases that often leads to severe otitis media with effusion. Further studies should be performed with larger numbers of specimens to confirm these findings.

ACKNOWLEDGMENTS — The authors thank Charles D. Bluestone, MD, Professor, and Eugene N. Myers, MD, Professor and Chairman, Department of Otolaryngology, University of Pittsburgh School of Medicine, for encouraging them to continue this project and for offering helpful criticism during this study.

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Ann Otol Rhinol Laryngol 100:1991

EPIGLOTTOPLASTY FOR RECONSTRUCTION OF POSTTRAUMATIC LARYNGEAL STENOSIS

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Laryngeal stenosis secondary to blunt laryngeal trauma is mostly localized at the supraglottic and glottic levels. The epiglottis is ideally suited to reconstruct the defect after excision of supraglottic and glottic scar tissue and anterior thyroid cartilage. It is the conclusion of the authors that epiglottic reconstruction is an effective procedure for repair of laryngeal stenosis at the supracricoid level. Two case reports are given.

KEY WORDS — epiglottoplasty, posttraumatic laryngeal stenosis.

INTRODUCTION

Numerous techniques are available for repair of a frontal thyroid defect when one needs a reconstruction procedure after excision of tumor or scar tissue. Only a few of them fulfill the prerequisites of laryngeal reconstruction: well-vascularized tissue that provides external support and at the same time an internal mucosal lining.[1]

Use of the epiglottis in reconstruction of a laryngeal stenosis after blunt laryngeal trauma is an excellent technique because of its elastic cartilage support and firmly attached mucosa. Downward mobilization of the epiglottis gives minimal aspiration problems postoperatively when both arytenoids are preserved. The use of the epiglottis as an advancement flap results in a reliable blood supply.[2] These advantages explain the popularity of the technique in reconstruction of frontal defects caused by a vertical laryngectomy for vocal cord cancer situated at the anterior commissure.

Most cases of posttraumatic laryngeal stenosis are a result of inadequate repair in the acute phase. Precise reapproximation of mucosa and cartilage immediately after trauma is an important factor in the prevention of late stenosis.[3]

Mobilizing the epiglottis in a posttraumatic larynx can be more difficult than after frontal laryngectomy. Comminuted fractures of the thyroid lamina are mostly accompanied by rupture of the thyroepiglottic ligament with superior retraction and fixation of the epiglottis in a more cranial and horizontal position (Fig 1D).

It is beneficial to have internal support after epiglottoplasty for some weeks in the severe forms of laryngeal stenosis, in order to retain the laryngeal lumen. A laryngeal stent should prevent scarring between endolaryngeal lacerations and maintain the internal configuration of the larynx. Hence, we performed the laryngoplasty in the first case over a soft laryngeal silicone stent.

This paper highlights the reliability of epiglottoplasty in cases of posttraumatic laryngeal stenosis repair. In the two patients, the epiglottoplasty was a second intervention. In an attempt to reconstruct the larynx in a first operation, a free graft of iliac crest bone was used. Both cases are an illustration of the theoretic prerequisites, absent in the first technique but present in the second, needed for a successful laryngeal reconstruction.

CASE REPORTS

Case 1. A 26-year-old man was admitted in December 1988 to a nearby hospital emergency room with severe laryngeal trauma and a mandibular fracture after a motorcycle accident. An urgent tracheotomy was necessary. After 2 weeks he was transferred to the University of Leuven for further care. An exploratory cervicotomy performed on January 2, 1989, indicated that the initial tracheotomy had been done through the multifragmented thyroid cartilage. The cannula was first replaced to the level of tracheal rings 2 and 3. Both vocal cords were luxated from the anterior commissure (Fig 1A). There was a rupture of the thyroepiglottic ligament with superior retraction of the epiglottis. The hypopharyngeal and ventricular band tears were approximated. The vocal cords were fixated laterally to the remnants of the thyroid cartilage. Because of the disrupted and displaced epiglottic cartilage, we preferred at that time to reconstruct the frontal thyroid defect with a free plate of bone from the iliac crest.

A Portex endotracheal tube, closed at the superior end, was inserted as a lumen-keeper. The petiole of the epiglottis was attached to the upper end of

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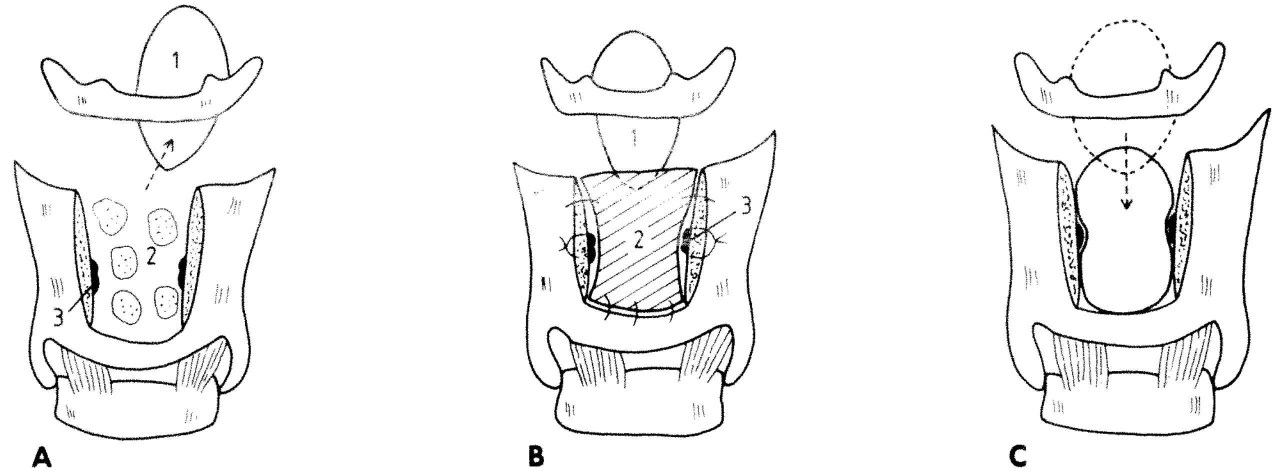

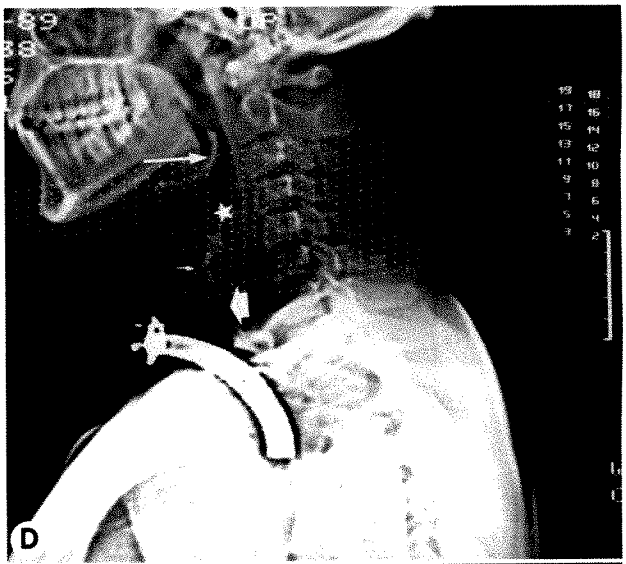

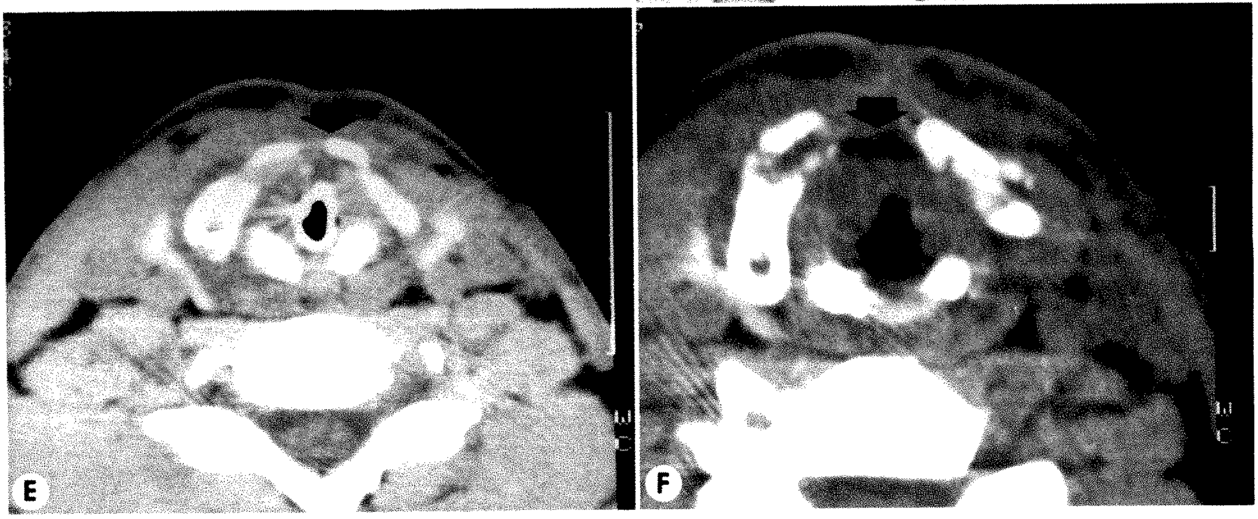

Fig 1. (Case 1) A) Multifragmented thyroid cartilage (2), with both vocal cords luxated from anterior commissure (3). 1 — superior retraction of epiglottis. B) Reconstruction with iliac crest bone (2) with reattached epiglottic cartilage (1) and laterally fixated vocal cords (3). C) Reconstruction with epiglottoplasty. D) Sagittal computed tomography (CT) scan after reconstruction with iliac crest: granulation tissue at supraglottic and glottic level (star); superior retraction of epiglottis (long arrow); intrusion of iliac crest graft into laryngeal lumen (short arrow) over caudally displaced laryngeal stent (large arrow). E) CT scan of laryngeal lumen at supraglottic level, obliterated with scar tissue and intrusion of iliac crest graft (arrow). F) CT scan of reconstructed larynx at glottic level. Note absence of calcification in elastic type of epiglottic cartilage. Arrow — epiglottis.

the avascular iliac crest bone (Fig 1B).

A computed tomography (CT) scan of the larynx 1 month postoperatively revealed a peripheral resorption of the iliac crest graft with intrusion into the laryngeal lumen. There was a total obstruction of the lumen above the laryngeal stent, which was displaced caudally, due to granulation and scar tissue formation (Fig 1D,E).

Indirect laryngoscopy revealed a total obstruction of the supraglottic inlet. Arytenoid movement could not be assessed. In October 1989 the granulation tissue and iliac crest graft were removed. We decided to perform a reconstruction with the epiglottis, which was mobilized downward as an ad-

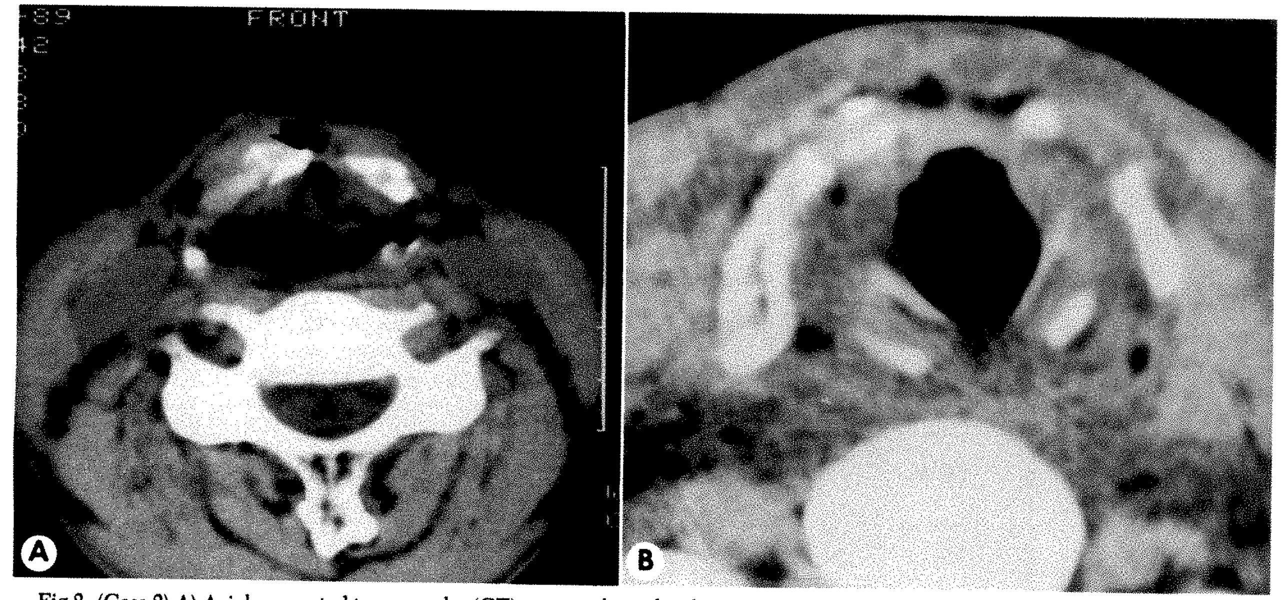

Fig 2. (Case 2) A) Axial computed tomography (CT) scan at glottic level reveals intrusion of iliac crest remnant with granulation tissue (arrow). B) CT scan at glottic level of reconstructed larynx after epiglottoplasty.

vancement flap to form the anterior laryngeal wall (Fig 1C). Before mobilizing the epiglottis into position between the thyroid lamina, we placed a laryngeal silicone stent in the endolarynx, extending above the false cords at its upper level and secured with sutures to the tracheal cannula. For maximum mobilization and descent, the epiglottis must be stripped entirely of its lingual perichondrium up to the tip, without penetration of the remaining mucoperichondrial attachments of the vallecula, as they provide the blood supply to the epiglottic flap. The surgical technique was described by Tucker et al.[4] The strap muscles were reapproximated and a drain was placed in the neck.

The soft silicone laryngeal stent was removed endoscopically 3 weeks postoperatively. A heavy silk loop passed through its upper segment during the reconstructive process is helpful at this stage. The nasogastric tube feedings were maintained for approximately 2 weeks postoperatively.

A CT scan displayed a sufficient laryngeal lumen (Fig 1F). The patient was able to swallow without aspiration and the tracheal cannula was removed 2 months postoperatively.

Case 2. A 43-year-old patient was referred to us in May 1989 with laryngeal stenosis. In November 1986, he had a car accident with blunt laryngeal trauma for which he was treated in a nearby hospital with a tracheotomy and reconstruction of the frontal thyroid defect with a free iliac crest graft. He had not been able to be decannulated since his operation. A laryngoscopy revealed a decreased sagittal glottic diameter, supraglottic scar tissue, and bilateral reduced arytenoid mobility with the right arytenoid in a more anterior position. A CT scan displayed a reduction of the sagittal laryngeal diameter, the remnants of the iliac crest anteriorly, and granulation tissue at the glottic and supraglottic levels with an inadequate airway (Fig 2A).

In December 1989 the iliac crest and granulation tissue were removed with repositioning of the right arytenoid cartilage. The frontal laryngeal defect was repaired with epiglottoplasty. A postoperative CT scan displayed a sufficient laryngeal lumen (Fig 2B). The tracheotomy tube could be removed after 1 month.

DISCUSSION

We here present two cases of laryngeal stenosis repair with epiglottoplasty. With this therapeutic approach, the reconstruction was successful in providing an airway not requiring a tracheotomy tube and a voice capable of communication.

The elastic epiglottic cartilage provides the support needed to maintain the laryngeal lumen during respiration. It is well vascularized and provides a mucosal internal lining membrane.

The first reconstruction in both cases with iliac crest graft was unsuccessful in accord with the theoretic considerations about laryngeal reconstruction. Peripheral resorption of the graft leads to intraluminal migration. The exposed bone, which lacks a blood supply, will behave almost like a foreign body and cause excessive granulation tissue formation and collagen deposition. The Portex endotracheal tube used in the first case to stabilize the iliac crest was an extra contribution in the scar tissue formation. Indwelling rigid round lumen-keepers that excoriate mucosal surfaces should be avoided.

Kennedy[5] described the use of the epiglottis to resolve a laryngeal stenosis secondary to cricothyroidostomy at the glottic and subglottic levels. In our limited experience epiglottoplasty has been proven to be a viable procedure in the management of chronic glottic and supraglottic stenosis after blunt laryngeal trauma.

CONCLUSION

Epiglottoplasty for reconstruction of a multifragmented thyroid cartilage unsuccessfully treated in the acute stage is an effective one-stage surgical approach. Good functional results with respect to respiration, deglutition, and phonation can be expected.

ACKNOWLEDGMENT — The authors thank Prof J. Tyberghein.

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Ann Otol Rhinol Laryngol 100:1991

LASER UVULOPALATOPLASTY IN TREATMENT OF HABITUAL SNORING

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Velopharyngeal sonorous snoring is best treated with uvulopalatopharyngoplasty (UPPP). To reduce surgical risks and minimize the morbidity, a simplified carbon dioxide laser uvulopalatoplasty (LUPP) was performed under local anesthesia. Among a total of 146 patients who had a LUPP performed, there was no significant bleeding or postoperative episodes of asphyxia. The procedure was well tolerated even by those patients with strong vomiting reflexes. The operation time was halved, as was the convalescence. Two patients (1.4%) developed scarring with nasal obstruction, but the impact of factors other than the laser approach itself seemed to be the cause. By scored questionnaires the effect on snoring, family complaints, and daytime somnolence was evaluated in two comparable random groups of patients. Sixty-three patients had LUPP procedures, and 37 had UPPP. The short-term results showed that about 90% of the patients considered themselves essentially improved as regarded snoring and that most patients felt more alert, irrespective of the surgical method used.

KEY WORDS — laser, snoring, uvulopalatopharyngoplasty.

INTRODUCTION

Habitual snoring, the most consistent symptom in sleep apnea syndrome, is considered a risk factor for development of hypertension, ischemic heart disease, and cerebrovascular disease,[1-4] although the association to hypertension has been questioned.[5] Snoring that is sonorous and habitual is also a problem in family life. Thus, snoring may qualify as a sociomedical diagnosis.

Snoring is best treated surgically.[6] The target is any part of the upper respiratory tract that contributes to sonorous snoring and respiratory obstruction, the velopharynx being the most prevalent one. The introduction of the refined uvulopalatopharyngoplasty (UPPP) in the treatment of snoring and sleep apnea syndrome[7] has markedly changed the well-being of these patients; the number of obstructive sleep apneas is significantly reduced in at least 50% of the patients with the syndrome, and the snoring is cured in almost all cases.[7-10] However, UPPP is not without risks. Most complications in these patients are confined to the impact of general anesthesia. Difficulties in postoperative arousal and respiration, cardiac arrythmia, postoperative confusion, and an unreliable airway all occur, especially in obese patients with sleep apnea. Even death due to postoperative asphyxia and bleeding has been reported. As a consequence of these risks and the fact that many otorhinolaryngology clinics are overwhelmed by patients with problem snoring, a simple, inexpensive surgical method associated with less risk is warranted.

Laser uvulopalatoplasty (LUPP) is a simplified surgical procedure that can be done under local anesthesia. The experience from 146 cases is reported with emphasis on surgical risks.

PATIENTS AND METHODS

Selection of Patients. Adult patients who complained of habitual sonorous snoring and disturbed relationships within the circle of family members or friends were considered for surgical treatment. Patients were admitted to the prospective part of the study if the snoring was generated mainly at the level of the velopharynx (1 case excluded), the distance between the faucial tonsils was more than 25 mm (26 cases excluded), and no simultaneous surgical procedures on the nose were performed (5 cases excluded). Patients complaining of habitual snoring and daytime sleepiness were also admitted, provided that no (<10) obstructive sleep apneas (>10 seconds) were disclosed in either of two sleep studies[11] (53 cases excluded). This selection generated a group of 70 patients from which the secretarial staff randomly selected cases for LUPP (33 cases) and conventional UPPP (37 cases), respectively. The laser group was then extended by 30 more consecutive cases that met the above criteria, for a total of 63 cases. The two treatment groups studied (Table 1) did not differ significantly from one another with regard to the distribution of sex, habitual sleep attacks, overweight, or hypertension. All patients considered for LUPP gave informed consent.

For evaluation of the surgical risks of LUPP, records and protocols were reviewed in 146 consecutive adult cases operated on at the clinic according to the method described.

Clinical Examination and Evaluation of Results. The configuration of the laryngeal introitus, tongue base, tonsils, velopharynx, and jaws was examined. A fiberoptic examination during voluntary snoring (Mueller maneuver) and a static cephalometry were performed.[12,13] Based on the findings, the generat-

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TABLE 1. STUDY GROUPS

	Female	*Age*		*Obesity**	*Hypertension†*
		Mean	*Range*		
Conventional UPPP (n = 37)	14%	47	30-74	31%	31%
LUPP (n = 63)	18%	45	24-70	27%	25%

UPPP — uvulopalatopharyngoplasty, LUPP — laser uvulopalatoplasty.

*Body mass index >29 kg/m².

†Receiving antihypertensive medication or having diastolic pressure >95.

ing level of snoring was established. The nasal cavity and nasopharynx were examined for additional obstruction. A four-point questionnaire was used for characterization of symptoms.[14] Before filling out the questionnaire the patients were asked to consult their spouses or friends and they were given a brief and uniform oral instruction on how to answer the questions. "Do you snore?" "Are your family or friends disturbed by your snoring?" and "Do you have daytime sleep attacks?" were the questions evaluated in particular. For follow-up, the patients were examined 3 to 4 months after the operation, and at that time an identical questionnaire was filled out. The importance of "nonrewarding" answers was pointed out. Complaints that shifted from "almost always" to "seldom" or "never," or from "often" to "never" were regarded as reflecting an essential improvement.

Surgical Techniques. As a result of patient selection, patients with a low palatal arch and/or lax posterior pillars and hypotrophic tonsils (Fujita IIa) predominated in both groups of patients. Conventional UPPP was performed essentially as previously described,[7] but the mucosal incisions were made with a cutting diathermy. The tonsils were removed irrespective of size. The LUPP was performed with a carbon dioxide laser, first with a Cooper Medical 30Z and a power of 25 to 35 W and later with a Sharplan 1025 and a power of 10 to 15 W. The extent of the excision was the same as with UPPP except for the tonsillectomy. The palatal excision was made below the level of the dimple of the palatal aponeurosis and was extended laterally through the base of the tonsillar pillars without cutting the palatopharyngeal muscles unless they were hyperplastic. In patients with a low palatal arch but a wide nasopharyngeal aperture the palatoplasty also included 3 to 4 mm of the anterior pillars. In patients with a narrow nasopharyngeal orifice and lax mucosa the posterior pillars were reduced and sutured laterally to stretch the oropharyngeal mucosa and to enlarge the aperture — a procedure involving the superior part of the tonsillar fossa. If redundant pharyngeal mucosa still remained, it was trimmed off by the laser down to the level of the epiglottic tip if necessary. In most patients just a couple of sutures were used bilaterally to approximate the mucosal edges of the two tonsillar pillars, but in other cases during the late phase of the study the palatal wound was also sutured with palatal nasopharyngeal mucosa saved for the purpose. At that phase of the study phenoxymethyl penicillin was introduced as prophylaxis.

TABLE 2. SHORT-TERM RESULTS

	Conventional UPPP	*LUPP*
Snoring		
Seldom or never	32/36 (89%)	51/60 (85%)
Often or always	4	9
Snoring that disturbed family		
Essentially improved	33/36 (92%)	56/60 (93%)
Slightly improved or unimproved	3	4
Habitual daytime sleep attacks		
Essentially improved or improved	10/13 (77%)	15/21 (71%)
Slightly improved or unimproved	3	6

UPPP — uvulopalatopharyngoplasty, LUPP — laser uvulopalatoplasty.

Except for the first patients operated on with laser (1986 and 1987), the patients had local anesthesia (105 cases) induced by 15 to 20 mL of lidocaine hydrochloride–epinephrine (10 mg/mL to 5 μg/mL) injected into the larynx after spraying with lidocaine aerosol. Morphine hydrochloride–scopolamine hydrobromide was used for premedication. The patients were operated on in a half-sitting position and had to wear tooth and eye protectors. Smoke was evacuated by a combined air evacuator and suction drain (to which a dressing may be attached to protect the posterior wall of the pharynx) via the nasal cavity or by a specially designed tongue depressor with suction capability.

RESULTS

Surgical Complications. Among a total of 146 patients who underwent LUPP — 105 under local anesthesia — no serious complications occurred during the operation or during the immediate postoperative phase. Neither troublesome bleeding nor postoperative episodes of asphyxia or confusion appeared, and no patient needed postoperative observation in the intensive care unit. In one case only the operation was incomplete because of strong vomiting reflexes. At follow-up 2 patients had developed a scar fibrosis with narrowing of the nasopharyngeal aperture and nasal obstruction. The scarring became even worse after reoperation with UPPP.

Clinical Efficiency of Each Procedure. There were 60 patients available for follow-up in the laser group, and 36 patients in the group subjected to conventional UPPP. The short-term results are shown in Table 2. In the laser group 51 patients (85%) reported a total or near-total elimination of sonorous snoring and 56 (93%) had received no complaints from family members. Of those who preoperatively had habitual daytime sleep attacks, 71% reported that these attacks essentially had disappeared. These results do not differ significantly from those found in patients operated on with the UPPP.

In the laser group 16 patients (27%) developed a slight or moderate scar fibrosis, compared to 5 patients (14%) in the UPPP group (χ^2, $p > .05$). Among patients in the second half of the laser series, 6 of 31 (19%) had a tendency toward scarring, compared to 10 of 29 early patients (34%) ($p > .05$). Despite some narrowing, no one experienced nasal obstruction, and all of these patients regarded themselves as essentially improved in regard to snoring.

DISCUSSION

Laser uvulopalatoplasty, intended for patients with obnoxious snoring generated at the level of the velopharynx, is a limited operation with less morbidity for patients than from conventional UPPP. Performed under local anesthesia, it is well tolerated by the patients. The postoperative pain is moderate and most patients can be discharged on the day of operation or the day after and return to work within a week or two. The method was not intended for patients with manifest sleep apnea syndrome.

Since tonsillectomy was not included in the laser procedure, only those patients without tonsillar hyperplasia were selected for comparison of the methods. Well above 70% of the patients considered for the study met this requirement and were potential candidates for LUPP. In patients with sleep apnea and a throat narrowed by obesity or tonsillar hyperplasia, a tonsillectomy is mandatory as an integrated part of UPPP. In snorers without these findings, tonsillectomy can be questioned, as the tonsils only indirectly contribute to sonorous snoring. When tonsillectomy was omitted, local anesthesia sufficed and postoperative morbidity was lessened. The average length of time for the surgical procedure was less than half that of UPPP. Under local anesthesia the patient's ability to snore could be tested and the palatal excision further extended if necessary. A laryngeal, hissing snoring ("hobby-saw" rather than "log-saw") was heard in some patients, and in these cases a fiberoptic examination combined with a Mueller maneuver was done. Redundant hypopharyngeal mucosa, tongue base hyperplasia, and a floppy epiglottis were occasionally seen, indicating a follow-up with whole-night polysomnography.

A four-point questionnaire was used for definition and evaluation of symptoms. Comparisons between studies based on questionnaires are hazardous, but for simultaneous comparing of two treatment modalities the questionnaire would be a reliable method. No recordings of snoring were done, since diagnosis and treatment indications should be based on the spouse's complaints and not on measured level or character of noise. Furthermore, patients who report that they snore habitually do snore objectively.[4]

Although laser-induced wounds heal more slowly than scalpel wounds,[15] tissue necrosis and postoperative edema were seldom seen except in cases of wound infection. This is in agreement with previous experience of oral laser surgery.[16] However, scarring seemed to be more prevalent among patients who underwent LUPP than in those who had UPPP. Factors that might have contributed to scarring were too high a laser power, too few sutures, and omission of antibiotic prophylaxis. (The last factor is indicated by a lower rate of scarring during the second half of the study.) A certain degree of scar tissue, however, might even stabilize the velopharynx and prevent snoring. Previously, oropharyngeal stenoses have been reported to occur after UPPP in sleep apnea patients, but there seemed to be no correlation between degree of scarring and sleep apnea response.[9] Nevertheless, three cases of severe narrowing and nasal obstruction have been observed at the clinic, two of them following laser procedures. That both patients became even worse after a wide scalpel excision of the scar tissue indicates that in cases of severe scarring biologic factors rather than the laser procedure itself were the main cause.

Although this is a preliminary report based on a rather small sample, no major differences were found in short-term results between LUPP and UPPP in regard to snoring. The results are also similar to those previously reported following UPPP.[7-10] Most patients with daytime sleep attacks felt essentially more alert after the operation, irrespective of the method used. Such attacks are prevalent in sleep apnea syndrome,[6-8] but few of the patients had any sleep apneas. Since false-negative findings may occur in sleep studies,[17] some patients might have had sleep apneas that disappeared postoperatively. However, the alertness may also be a consequence of less disturbed bed partners and hence fewer sleep interruptions.

In the surgical treatment of patients with obnoxious snoring, 5 years of experience with LUPP has produced short-term results beyond expectations. The approach under local anesthesia seems to be a relatively safe method and a valuable complement to conventional UPPP, with the potential of reducing morbidity and costs to the patients.

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INHIBITION OF BACTERIAL ADHERENCE BY NASOPHARYNGEAL SECRETIONS

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The role of secretory immunoglobulin (Ig) A in nasopharyngeal secretions in the adherence of *Streptococcus pneumoniae* and *Hemophilus influenzae* to nasopharyngeal epithelial cells was investigated in vitro. The adherence was remarkably reduced by treating bacteria with nasopharyngeal secretions, and the antiadhesive activity was significantly greater in nasopharyngeal secretions having secretory IgA antibody activity against bacteria than in those having no activity. Noticeable changes were not observed in the antiadhesive activity caused by absorption of IgG from nasopharyngeal secretions. Results suggest that secretory IgA in nasopharyngeal secretions is related to bacterial adherence and adds to the prevention of nasopharyngeal infections.

KEY WORDS — bacterial adherence, *Hemophilus influenzae*, nasopharynx, secretory IgA, *Streptococcus pneumoniae*.

INTRODUCTION

The mucosal membrane of the upper respiratory tract is always exposed to pathogenic bacteria and to other antigenic insults. Bacterial adherence to mucosal surfaces is an initial step in the infection of the underlying tissue. Previously we reported that the adherence of *Streptococcus pyogenes* to nasal mucosal cells is significantly increased in patients with chronic sinusitis as compared with normal subjects.[1] We also reported that the adherence of *Hemophilus influenzae* to nasopharyngeal mucosa is significantly higher in children with otitis media with effusion (OME) than in control children.[2] These findings suggest that bacterial adherence plays an important role in the establishment of upper respiratory tract infections.

The mucosal surfaces have remarkable barriers against invading bacterial pathogens. Bacterial adherence may be influenced by various components in mucosal secretions, such as antibodies and glycoprotein. Secretory immunoglobulin (Ig) A is the most predominant immunoglobulin in external secretions, playing an important role in mucosal infections. Williams and Gibbons[3] found that secretory IgA isolated from parotid fluid specifically decreased the adherence of *Streptococcus* strains to human buccal epithelial cells. The adhesion of *Escherichia coli* to human urinary tract epithelial cells was inhibited by secretory IgA fraction of urine from patients with acute pyelonephritis.[4] Secretory IgA is found in nasopharyngeal secretions in high concentration.[5] However, it remains unclear whether secretory IgA in nasopharyngeal secretions inhibits bacterial adherence to nasopharyngeal mucosa.

In the present study, the adherence of *Streptococcus pneumoniae* and *H influenzae*, which are commonly considered pathogens of OME,[6] to nasopharyngeal epithelial cells was studied in vitro, and the role of secretory IgA in nasopharyngeal secretions was investigated.

MATERIALS AND METHODS

Bacteria. Nontypeable *H influenzae* and *S pneumoniae* type 3, isolated from the nasopharynx of children with OME, were used for the adherence test. These strains were stored in 20% skim milk at −80°C. One of the stored samples was thawed for each test. *Hemophilus influenzae* was cultured on chocolate agar plate overnight and transferred to tryptic soy broth containing 5% Fildes enrichment (Difco, Detroit, Mich). After 6 hours of incubation at 37°C, the bacteria were harvested by centrifugation and suspended in phosphate-buffered saline solution (PBS; 0.15 mol/L NaCl, 0.01 mol/L PO4, pH 7.4) at a concentration of 2×10^9/mL. *Streptococcus pneumoniae* was cultured on blood agar plate, grown in tryptic soy broth, and resuspended in PBS at a concentration of 2×10^8/mL.

Nasopharyngeal Secretions and Colostral Secretory IgA. Specimens of nasopharyngeal secretions were obtained by aspiration from 49 normal children 4 to 12 years of age and free from symptoms of ear, nasal, and the other respiratory infectious diseases. Approximately 100 µL of nasopharyngeal secretion was collected from each subject. The specimens were stored at −80°C. Samples were thawed and diluted five times with PBS. After centrifugation, the supernatants were collected. Secretory IgA antibody activity against *H influenzae* or *S pneumoniae* was determined by enzyme-linked immunosorbent assay (ELISA), described by Yamaguchi et

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BLOCKING EFFECT OF VARIOUS AGENTS FOR NONSPECIFIC BINDING OF BACTERIA

Blocking Agent		*Inhibition of Binding (%)* S pneumoniae *(10^8/mL)*	H influenzae *(10^9/mL)*
Bovine serum albumin	5%	83	81
	2.5%	81	80
Gelatin	1%	36	66
Hemoglobin	5%	32	69

Percentage of inhibition = (1 − [values of blocked wells/values of unblocked wells]) x 100.

al,[7] by the use of formaldehyde solution–treated whole cells of bacteria as solid-phase antigens. Horseradish peroxidase–conjugated rabbit anti human secretory component (DAKO, Glostrup, Denmark) and horseradish peroxidase–conjugated goat anti human IgA (TAGO, Burlingame, Calif) were used to detect secretory IgA antibody activity. *o*-Phenylenediamine was used for substrate. Absorbance was measured by spectrophotometry at 492 nm. To investigate the role of IgG in bacterial adherence, IgG was removed from nasopharyngeal secretions having secretory IgA and IgG activity against *S pneumoniae* or *H influenzae* by affinity chromatography with the use of staphylococcal protein A Sepharose CL-4B (Pharmacia Fine Chemicals, Uppsala, Sweden). The material passing through the column was dialyzed and concentrated to one half of the original sample volume. The absorption of IgG was checked by immunodiffusion analysis.

Secretory IgA in human colostrum was purified according to a method earlier described by Mogi.[8] After centrifugation to remove fat and casein, the supernatant was immediately adjusted to pH 7.0 with 1N NaOH solution precipitated with 50% saturated ammonium sulfate. The precipitate was dialyzed and applied to diethylamino-ethyl-cellulose (Pharmacia Fine Chemicals) column chromatography. The eluate of 0.1 mol/L phosphate buffer (pH 6.4) containing secretory IgA was dialyzed and concentrated. The antibody activity against *S pneumoniae* and *H influenzae* was estimated in the same way as in nasopharyngeal secretions.

Preparation of Nasopharyngeal Epithelial Cell Suspension. Nasopharyngeal epithelial cells were collected from 43 normal children 5 to 7 years of age by swabbing the nasopharynx with a cotton-tipped wooden swab. The swabs were vigorously stirred in PBS to release the cells. The epithelial cells were washed and suspended in PBS that contained 10^5 cells per milliliter.

Adherence Assay In Vitro. The ELISA technique elaborated by Ofek et al[9] was employed to investigate the role of secretory IgA in nasopharyngeal secretions. Microtiter plate (Dynatech, Chantilly, Va) was activated with 1 mol/L lysin solution and 1.25% glutaraldehyde solution. A nasopharyngeal epithelial cell suspension (100 μL) was added to each well and allowed to settle for 10 minutes at room temperature. After the plate was centrifuged for 20 minutes at 300g, the supernatant was aspirated and then dried overnight at 37°C. The unoccupied plastic space in wells containing immobilized epithelial cells was blocked by incubation with 100 μL of 5% bovine serum albumin (BSA) for 3 hours at 37°C. The wells were then washed four times with PBS. Fifty microliters of a bacterial suspension and 50 μL of a sample of nasopharyngeal secretions or secretory IgA purified from colostrum were added to each well. The microtiter plate was incubated for 1 hour at 37°C. After washing five times with PBS, the plate was fixed by heating at 65°C for 10 minutes. Rabbit antibacterial serum, prepared by intravenous injection with gradually increasing doses of 0.5% formalin-killed bacteria, was diluted 1:100 in 5% BSA, applied to each well, and incubated for 1 hour at 37°C. The plate was washed again five times with PBS. Horseradish peroxidase–conjugated goat anti rabbit IgG (Cappel, West Chester, Pa), diluted 1:1,000 in 5% BSA, was added to each well and incubated for 1 hour at 37°C. After washing five times, 100 μL of *o*-phenylenediamine as substrate was added to each well. The color was allowed to develop for 15 minutes at room temperature, and the reaction was stopped with 2.5 mol/L sulfuric acid. Absorbance was measured by spectrophotometry at 492 nm. Samples

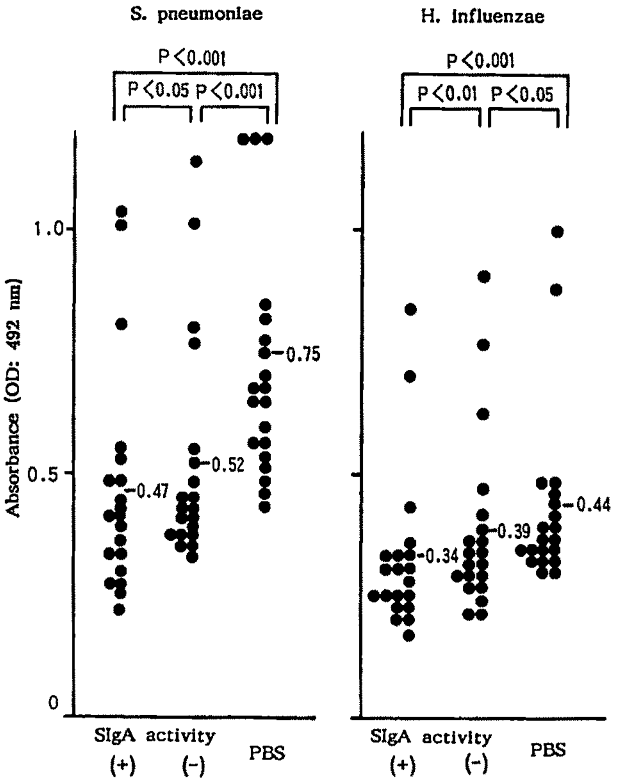

Fig 1. Inhibition of bacterial adherence by nasopharyngeal secretions. Adherence of *S pneumoniae* and *H influenzae* was lowest in subjects treated with nasopharyngeal secretions having secretory IgA (SIgA) antibody activity. OD — optical density, PBS — phosphate-buffered saline.

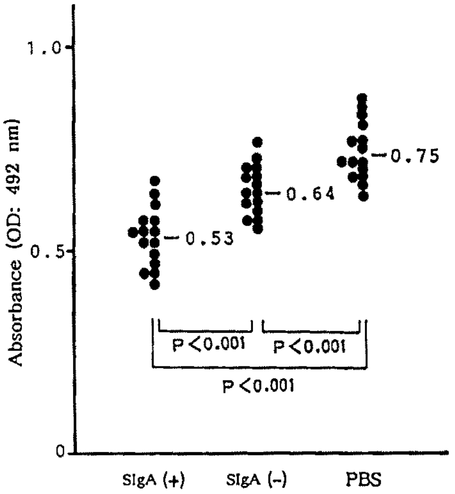

Fig 2. Inhibition of bacterial adherence by secretory IgA (SIgA) in human colostrum. Adherence of *S pneumoniae* was most efficiently reduced by secretory IgA having antibody activity. OD — optical density, PBS — phosphate-buffered saline.

were evaluated in duplicate. Controls consisted of wells without bacteria and wells without immobilized epithelial cells. Student's *t* test was used to calculate the statistical significance of the data.

RESULTS

To estimate the specific adherence of bacteria to immobilized epithelial cells, it is necessary to rule out nonspecific binding of bacteria to the wells of the ELISA plate. Bovine serum albumin (5% and 2.5%), gelatin (1%), and hemoglobin (5%) were tested for the ability to block that binding to activated plastic without epithelial cells. It is desirable that the blocking agent have little effect on specific adherence to immobilized cells. As shown in the Table, BSA had high blocking ability and the ability was higher in 5% BSA than in 2.5% BSA. Therefore, 5% BSA was used for the blocking agent in the adherence assay of both *S pneumoniae* and *H influenzae*. The blocking ability of 5% BSA was 83% for 10^8/mL of *S pneumoniae* and 81% for 10^9/mL of *H influenzae* as calculated with the formula reported by Ofek et al.[9]

Nasopharyngeal secretions that had secretory IgA antibody titers of more than 1:1,280 and those lower than 1:10 were used to investigate the antiadhesive effect of secretory IgA. The ELISA values for adherence of *S pneumoniae* and *H influenzae* and the effect of nasopharyngeal secretions are shown in Fig 1. Both mean ELISA values of the groups treated with nasopharyngeal secretions were significantly lower than that of the group treated with PBS. In those three groups, the mean value was the lowest in the group treated with nasopharyngeal secretions having high secretory IgA antibody activity against bacteria. This finding was observed in adherence of both *S pneumoniae* and *H influenzae*.

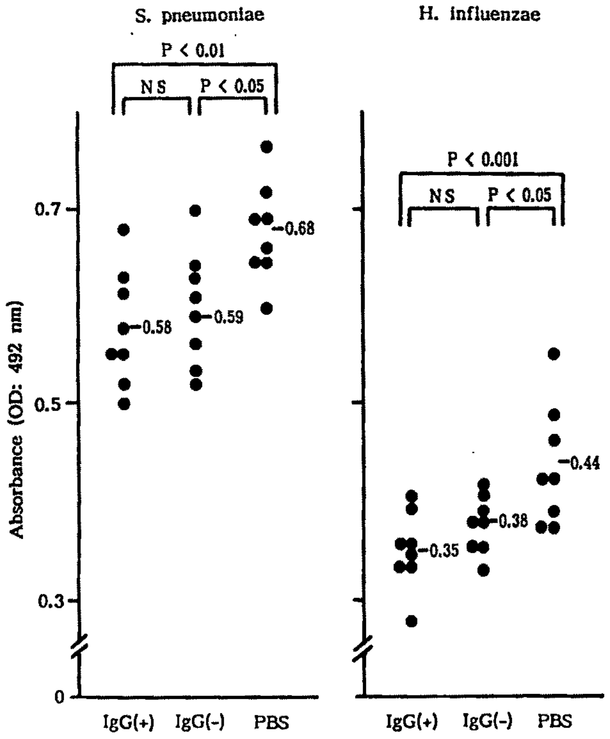

Fig 3. Inhibition of bacterial adherence by nasopharyngeal secretion after absorption of IgG. There was no significant difference between subjects treated with nasopharyngeal secretions having IgG and those treated with secretions absorbed of IgG. NS — not significant, OD — optical density, PBS — phosphate-buffered saline.

Two of 18 samples of secretory IgA, purified from human colostrum, had antibody activity against *S pneumoniae*. No sample had any activity against *H influenzae*. Therefore, the effect of secretory IgA in colostrum regarding the adherence of *S pneumoniae* was estimated. As shown in Fig 2, the mean ELISA value was significantly lower in the group treated with secretory IgA having antibody activity than in the group treated with secretory IgA without activity. Each mean value of both subjects treated with secretory IgA was significantly lower than that of the subjects treated with PBS.

The antiadhesive effect of nasopharyngeal secretions after absorption of IgG is shown in Fig 3. Each mean ELISA value of the groups treated with nasopharyngeal secretions was significantly lower than that of the group treated with PBS. However, there was no significant difference between the group treated with nasopharyngeal secretions having IgG and that treated with secretions absorbed of IgG.

DISCUSSION

It has been demonstrated that secretory IgA serves a protective function against viral infections.[10] However, the mechanism against a bacterial infection is only partly understood. Gregory and Filler[11] indicated that the number of viable *Streptococcus mutans* organisms in dental plaque and whole saliva decreases following oral immunization with S *mutans*, which correlates with increased levels of IgA antibodies in saliva. Secretory IgA isolated from parotid fluid and urine inhibits bacterial adherence.[3,4] In the present study, the antiadhesive activity of secretory IgA in nasopharyngeal secretions was investigated by use of the ELISA technique. The ELISA value was significantly lower in the group treated with nasopharyngeal secretions having high secretory IgA antibody activity than in the group treated with secretions having no activity. The findings suggest that secretory IgA may be related to the reduced adherence of *S pneumoniae* and *H influenzae* by nasopharyngeal secretions.

Antiadhesive activity of secretory IgA purified from colostrum against *S pneumoniae* was the highest in secretory IgA with specific activity. However, the adherence was also reduced in the absence of specific activity. This result suggests that the adherence might be inhibited by nonspecific secretory IgA and certain contaminated substances. The same finding was observed in the inhibition by nasopharyngeal secretions. Andersson et al[12] investigated the antiadhesive effect of milk against *S pneumoniae* and *H influenzae*, and suggest that the inhibition is mainly due to components other than specific antibodies. Some oligosaccharides are known to act as receptors and inhibit the adherence of *S pneumoniae*.[12] From these findings it is supposed that nasopharyngeal secretions contain several factors besides secretory IgA that participate in the adherence of *S pneumoniae* and *H influenzae*.

Svanborg-Edén and Svennerholm[4] reported that IgG in urine has antiadhesive activity against *E coli*. However, commercially available gammaglobulin with a high antibody titer was only slightly more effective than milk in blocking the adherence. In the present study, the antiadhesive effect of nasopharyngeal secretions was not affected by absorption of IgG. The results suggest that IgG in nasopharyngeal secretions is less effective than secretory IgA in inhibiting bacterial adherence. Because increased adhesion was observed with a certain concentration of gammaglobulin,[4] there might be some differences between IgG and secretory IgA in the function sites and mechanism for antiadhesive activity.

In summary, the present study shows that adherence of *S pneumoniae* and *H influenzae* to nasopharyngeal epithelial cells is inhibited by nasopharyngeal secretions. The antiadhesive activity of nasopharyngeal secretions is increased by the presence of specific secretory IgA. Nasopharyngeal colonization is inhibited by several components in nasopharyngeal secretions, and secretory IgA may add to the prevention of nasopharyngeal infections.

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Ann Otol Rhinol Laryngol 100:1991

HEARING AND VESTIBULAR DISTURBANCES IN BEHÇET'S SYNDROME

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In order to evaluate the prevalence of audiovestibular disturbances in Behçet's syndrome, we submitted 20 consecutive patients and 20 control subjects to detailed audiologic and vestibular examination in the last 3 years. A sensorineural hearing loss was found in 12 patients, 2 of whom revealed sudden deafness. Two other patients with neuro-Behçet's syndrome showed a vestibular function deficit, and 3 others exhibited altered caloric stimulation test results. Two of these last patients also revealed a simultaneous bilateral auditory deficit. HLA typing showed the presence of the B51 antigen in 10 of the 14 patients with ear involvement, while only 3 of the 6 patients without ear involvement were HLA-B51-positive. Results suggest that audiovestibular involvement is common in Behçet's syndrome: sudden deafness may be the first sign of ear disturbance; vestibular lesions may represent an early sign of neuro-Behçet's syndrome; and the HLA-B51 antigen is associated with ear involvement. Otoneurologic study can reveal hidden brain stem lesions in Behçet's patients during flare-ups of the disease, even without obvious signs of neurologic deficits.

KEY WORDS — audiometry, Behçet's syndrome, dizziness, hearing loss, HLA antigens, vestibular function tests.

The syndrome of aphthous ulceration, genital ulceration, and iridocyclitis was described for the first time by Hippocrates in the fifth century BC.[1] However, it was not until Behçet's papers[2,3] that the syndrome attracted attention in the medical world. Since Behçet's description, a large number of manifestations have been added. Cutaneous, central nervous system (CNS), vascular and cardiovascular, gastrointestinal, renal, and pleuropulmonary lesions, arthritis, and epididymitis are today accepted as additional clinical features of Behçet's syndrome.[4] Auditory and vestibular lesions, among the clinical manifestations of CNS involvement, were first described by Alajouanine et al[5] in 1961. Since then, other authors have shown that hearing loss and dizziness are frequent symptoms in patients affected by Behçet's syndrome with or without the involvement of the CNS.[5-9] Only two studies exist in the literature on the frequency of ear involvement, both in series of 16 patients.[6,7] As these reports lack a control group and their results do not entirely agree, we decided to verify, in a controlled study, the prevalence of audiologic and vestibular disturbances in an unselected series of Behçet's patients over a 3-year period of follow-up.

PATIENTS AND METHODS

Twenty consecutive patients with definite Behçet's syndrome according to the criteria of Mason and Barnes[10] attending the Rheumatic Disease Unit have undergone detailed audiologic and vestibular evaluation at the Department of Otolaryngology since 1986. They included 14 men and 6 women whose mean age was 37.8 years (SD, 11.1 years; range, 21 to 63 years) and mean disease duration was 11.3 years (SD, 8.6 years; range, 3 to 29 years). Clinical data and HLA typing (B locus) of all 20 patients are shown in Table 1. Twenty hospital staff members (12 men and 8 women) consented to serve as controls. None of these subjects had ever suffered from any rheumatic disease or vasculitis syndrome involving the inner ear. Their mean age was 43.1 years (SD, 8.8 years; range, 25 to 60 years). All patients were questioned about any history of audiovestibular disturbances, cranial trauma, ear infection, dysmetabolic conditions, ototoxic drug use, exposure to noise, and other agents that might have caused ear damage. After a complete otologic examination, audiologic evaluation was performed in all patients by pure tone audiometry (0.25, 0.5, 1, 2, 3, and 4 kHz), speech audiometry obtained by use of phonetically balanced lists of 10 bisyllabic words,[11] impedance audiometry, stapedius reflex threshold with contralateral stimulation, recruitment investigation using Metz's[12] test, the reflex decay test of Anderson et al,[13] and brain stem response audiometry[14] (Table 2). The vestibular function was studied by evaluation of spontaneous, positional, cervical, and head-shaking nystagmus,[15] caloric stimulation using the method of Fitzgerald and Hallpike,[16] and the visual suppression test.[17] All these vestibular investigations were performed under a simultaneous electronystagmographic recording. The normal range was calculated for each single test on the basis of 40 normal subjects by the audiologic and vestibular laboratories of the Institute of Otolaryngology of Pisa University. After the first evaluation, all Behçet's patients were checked every year by audio-

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TABLE 1. CLINICAL MANIFESTATIONS AND HLA TYPING (B LOCUS) IN 20 PATIENTS WITH BEHÇET'S SYNDROME

Pt No.	*Age (y)*	*Sex*	*Disease Duration (y)*	*Oral Ulcers*	*Genital Ulcers*	*Eye Lesions*	*Skin Lesions*	*Arthritis*	*Ear Involvement*	*Other Manifestations*	*HLA (B locus)*
1	33	M	13	+		Uveitis (A, P)	Pyoderma	+			27, 58
2	37	M	9	+	+	Uveitis (A, P)	Erythema nodosum, pyoderma	+	Auditory	Epididymitis	51, 57
3	28	M	9	+	+	Uveitis (A, P)	Erythema nodosum, pyoderma, pathergy	+	Vestibular	Epididymitis, thrombophlebitis, neuro-Behçet's syndrome	8, 51
4	40	M	29	+		Uveitis (A, P)	Erythema nodosum, pyoderma, pathergy	+	Auditory	Epididymitis, thrombophlebitis	51
5	32	M	7	+	+	Uveitis (P)	Pyoderma		Auditory		51
6	40	M	9	+	+	Uveitis (A, P)	Pyoderma	+	Auditory	Epididymitis	16, 35
7	33	M	7	+	+		Erythema nodosum, pyoderma			Epididymitis, thrombophlebitis	51
8	52	M	4	+		Uveitis (A, P)	Pyoderma	+	Auditory		42, w57
9	21	M	7	+	+		Erythema nodosum, pyoderma, pathergy		Auditory	Epididymitis, retrobulbar neuritis	12, 35
10	56	F	29	+			Pyoderma	+	Auditory, vestibular	Thrombophlebitis	8, 51
11	27	M	6	+		Papilledema	Pyoderma		Vestibular	Neuro-Behçet's syndrome	18, 51
12	45	M	18	+	+	Uveitis (A, P)			Auditory		51
13	63	F	6			Uveitis (A)	Erythema nodosum	+	Auditory	Pericarditis, myositis	18, w53
14	46	F	20	+	+		Erythema nodosum, pyoderma, pathergy		Auditory		51, 12
15	48	M	28	+	+	Uveitis (A, P)	Erythema nodosum, pyoderma, pathergy		Auditory, vestibular	Epididymitis, retrobulbar neuritis	51
16	39	M	7	+	+		Erythema nodosum			Epididymitis, thrombophlebitis,	51
17	25	M	4	+	+	Uveitis (A, P)	Erythema nodosum			Epididymitis	17, 35
18	34	F	4	+	+		Pyoderma, pathergy	+	Auditory		55
19	23	F	3	+	+		Erythema nodosum, pyoderma	+	Vestibular		51
20	35	F	8	+	+	Uveitis (P)	Erythema nodosum, pyoderma, pathergy				35

A — anterior, P — posterior, pathergy — polyvalent allergy.

gram, while the vestibular function was evaluated only in patients complaining of vertigo attacks.

RESULTS

The initial interview with a physician regarding subjective symptoms revealed that 16 patients in the Behçet's group had had audiovestibular complaints. Eight of these complained of hearing loss, 3 of dizziness without any audiologic symptoms, and 5 of both auditory and vestibular disturbances. None reported cranial trauma, ear infection, dysmetabolic conditions, or ototoxic drug use, and only 1 patient had a history of exposure to noise. Five control patients reported audiovestibular symptoms: 2 complained of hearing loss and/or tinnitus, and 3 of dizziness. One of the 2 with hearing loss had had a cranial trauma together with a history of exposure to noise. Audiologic and vestibular investigation revealed abnormalities in 15 Behçet's patients and in 3 control patients, whereas normal values were found in the rest. The mean ages of the Behçet's patient groups with and without ear involvement were 38.5 and 36.1 years, respectively ($p > .05$), and the mean disease durations were 13.1 and 7.1 years ($p > .05$).

Hearing. The audiologic evaluation showed moderate to severe sensorineural hearing loss (>35 dB

TABLE 2. PARAMETERS AND TECHNICAL DETAILS OF BRAIN STEM RESPONSE AUDIOMETRY

Apparatus	Amplaid MK 15
Click polarity	Rarefaction
Width	100 microseconds
Repetition rate	21 per second
Headphones (telephonics)	TDH 49
Electric impedance	<1 kΩ
Filter pass band	100 to 2,500 Hz
Number of runs	2,000
Artifact rejection criteria	10 μV/division
Stimulus intensity	100 dB sound pressure level peak equivalent
Masking (contralateral)	60 dB sound pressure level
Electrode placement	Vertex of mastoid — front of patient's head
Analysis time	12 milliseconds

hearing level in at least two frequencies) in 12 of the 13 Behçet's patients who had complained of auditory disturbances (Table 3). Hearing loss was unilateral in 4 and bilateral in 8. One of these 12 (patient 6) experienced sudden bilateral deafness and another (patient 13) a sudden unilateral deficit. There was no typical audiogram in these Behçet's patients. Speech audiometry failed to reach 100% at 30 dB sound pressure level in all 12 patients. The tympanogram did not show a conductive deafness, while the recruitment investigation test and brain stem response audiometry confirmed cochlear involvement in all 12 patients. Chronic exposure to noise might have caused a bilateral, symmetric hearing loss, with a preponderance for high tones, in 1 of the 12 (patient 8). A moderate deafness was evident in only 2 control patients; in 1 of these, exposure to noise caused a bilateral, symmetric hearing deficit.

Vestibular Function. Five of the eight patients who complained of attacks of vertigo showed altered vestibular test values (Table 4). Caloric stimulation tests revealed a vestibular deficit in two patients and a bilateral decreased response in two others. One of these last two (patient 11), during hospitalization in the Neurology Department of Pisa University 4 years before due to a sudden hemiparesis from neuro-Behçet's syndrome, had shown a spontaneous and positional nystagmus, together with a bilateral vestibular deficit after caloric stimulation tests. An acute vestibular syndrome was also evident in patient 3, who had complained of dizziness during a flare-up of Behçet's syndrome. Evaluation of vestibular function showed a positional nystagmus, positive head-shaking test results, a pure directional preponderance, and negative visual suppression test results. These last two findings, together with the clinical picture (retinal vasculitis and meningoencephalitis), suggested the involvement of the central vestibular tracts. A bilateral vestibular deficit was evident in only one control patient after caloric stimulation tests.

HLA Typing. HLA typing revealed the presence of the B51 antigen in 12 Behçet's patients and 2 controls ($p < .001$). Among the patients, the B51 antigen was found in 10 of the 14 with ear involvement, while only 2 of the 6 without ear involvement were positive for the B51 antigen.

Natural Course. Eighteen of the 20 Behçet's patients followed up over a 3-year period have not complained of vestibular symptoms or shown any significant modification of auditory threshold (>10 dB hearing level at each frequency). Patient 6, who presented with sudden deafness, rapidly improved and completely recovered his hearing function with high-dose methylprednisolone therapy. Patient 3, who showed an acute vestibular syndrome, recovered his vestibular function completely with immunosuppressive (cyclosporine) and plasmapheretic therapy that was given when methylprednisolone alone did not improve the vasculitis.

DISCUSSION

Behçet's syndrome is a multisystemic disorder that may involve, through a relapsing vasculitis, a

TABLE 3. AUDIOLOGIC FINDINGS

Pt No.	*Pure Tone Audiometry (kHz)*												*Speech Audiometry*		*Stapedius Reflex Threshold (kHz)*							
	0.25		*0.5*		*1.0*		*2.0*		*3.0*		*4.0*				*0.5*		*1.0*		*2.0*		*4.0*	
	R	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*
2	20	60	15	60	15	65	25	55	20	60	20	60		+	80	100	80	105	85	95	90	105
4	15	20	15	10	10	10	20	30	35	40	40	45		+	95	95	85	85	90	90	100	105
5	20	35	15	35	10	30	10	30	10	40	15	45		+	90	100	75	85	80	85	85	85
6	30	50	30	65	35	75	50	75	60	75	60	80	+	+	95	110	95	105	100	100	–	115
8	10	10	10	10	10	15	80	65	80	75	80	90	+	+	90	80	90	80	115	110	–	–
9	5	10	0	10	10	10	10	25	5	35	5	40		+	85	95	90	90	90	85	90	90
10	35	15	35	20	40	20	40	25	50	40	50	45	+	+	90	85	90	85	95	90	100	85
12	10	15	10	15	10	10	35	30	45	45	50	50	+	+	105	90	90	85	85	90	100	100
13	10	75	10	70	10	65	10	60	10	60	10	50		+	90	105	90	100	100	95	105	115
14	10	15	10	10	10	10	30	30	35	40	40	45	+	+	80	80	75	75	80	75	90	90
15	10	70	10	65	5	70	20	85	35	80	40	80		+	85	110	95	110	95	115	100	125
18	20	20	20	20	20	20	30	35	45	35	50	40	+	+	90	95	85	90	90	90	95	95

All patients had negative results on Anderson's reflex decay test.

Plus — abnormal results on speech audiometry, minus — lack of stapedius reflex.

TABLE 4. ELECTRONYSTAGMOGRAPHIC FINDINGS

Pt No.	*Eye Pursuit*	*Nystagmus*			*Head-Shaking Test*	*Caloric Vestibular Stimulation Tests*			
		Spontaneous	*Positional*	*Cervical*		*VP*	*DP*	*BDR*	*VST*
3	N	–	+	–	+	–	+	–	–
10	N	–	–	–	–	+	–	–	+
11	N	–	–	–	–	–	–	+	+
15	N	–	–	–	–	+	–	–	+
19	N	–	–	–	–	–	–	+	+

N — normal, VP — vestibular paresis, DP — directional preponderance, BDR — bilateral decreased response, VST — visual suppression test, plus — positive response, minus — negative response.

large number of organs.[4] Involvement of the audiovestibular system has been reported by many authors[6-9] since the first description by Alajouanine et al,[5] who described hearing loss and gaze paretic nystagmus in a patient suffering from meningoencephalitis. Only two studies, both lacking a control group, exist in the literature on the prevalence of audiovestibular disturbances in Behçet's syndrome.[6,7] Brama and Fainaru[6] first described 10 subjects with audiovestibular complaints in a series of 16 patients without CNS involvement. Four showed a progressive sensorineural hearing loss, 1 a peripheral vestibular syndrome, and 5 both acoustic and peripheral vestibular deficits. Audiologic and vestibular evaluation revealed cochlear and vestibular abnormalities, and the authors suggested that vasculitis from Behçet's syndrome may underlie audiovestibular dysfunctions. The second report was made by Belkahia et al[7]: in a selected series of 16 patients, 8 were followed at the Department of Neurology as a result of CNS disturbances (neuro-Behçet's syndrome), and a high prevalence of vestibular disorders was found. All of these 8 patients revealed central vestibular damage, and 5 of the other 8 showed peripheral vestibular involvement. Hearing loss was found in only 2 of the 8 patients with a central vestibular syndrome.

Our study shows a significantly high involvement of the audiovestibular system in Behçet's patients in comparison with the control group, and demonstrates a more frequent hearing deficit (12 patients with unilateral or bilateral hearing loss) compared with vestibular system damage (5 patients). Audiologic tests revealed that the sensorineural deafness was due to a lesion located in the cochlea. Vestibular function studies furthermore showed that Behçet's syndrome may cause a peripheral lesion more frequently than damage to the central vestibular tracts. These last findings may be explained by the fact that only 2 patients in our study were affected by neuro-Behçet's syndrome, and thus the vasculitis could be expected to involve the central vestibular tracts that run widely through the brain stem only in these cases. The higher prevalence of the central vestibular syndrome in the study of Belkahia et al[7] compared with our results and those of Brama and Fainaru[6] can be explained by the presence in their series of 8 patients with CNS involvement. In contrast with the reports of Brama and Fainaru,[6] we did not find that ear involvement was statistically correlated with age or disease duration, nor that audiovestibular damage was progressive in our series over a 3-year period of follow-up. The only 2 patients who had an acute ear involvement promptly improved and completely recovered from their audiovestibular deficit with methylprednisolone and/or immunosuppressive and plasmapheretic therapy.

In conclusion, as shown by our results and in agreement with the data found in the literature, 1) audiovestibular involvement in Behçet's syndrome is frequent and generally underestimated; 2) the cochlea is more frequently involved than the vestibular labyrinth or the central vestibular tracts; 3) sudden deafness may be the first sign of audiologic involvement; 4) a vestibular deficit may represent an early sign of neuro-Behçet's syndrome; and 5) the HLA-B51 antigen is associated with ear involvement, in agreement with Inaba's[18] findings for neuro-Behçet's syndrome. As central vestibular tract involvement may represent a manifestation of hidden brain stem lesions,[18] we propose an otoneurologic study in all Behçet's patients during flare-ups of the disease, even when there is no clear involvement of the CNS.

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CARE OF THE PROFESSIONAL VOICE

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Ann Otol Rhinol Laryngol 100:1991

EFFECT OF CYCLOSPORINE A ON THE HEARING LOSS IN BEHÇET'S DISEASE

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Thirty-five patients with Behçet's disease (20 under cyclosporine A [CyA] treatment and 15 under the conventional therapy), 12 patients suffering from endogenous uveitis, and 35 normal subjects were evaluated audiologically before entering the study and were followed up for at least a year. Twenty-eight Behçet patients (80%) showed some degree of hearing loss. The averaged pure tone audiogram of the Behçet group showed statistically significant auditory deficits in comparison with that of the control group. None of either the Behçet group or the uveitis group showed any hearing deterioration during the follow-up period. Five Behçet patients under CyA therapy demonstrated improvement in their hearing. The difference between the two groups of Behçet patients (CyA versus conventional treatment) was found to be statistically significant ($p < .05$). Thus, CyA might serve as an important mode of treatment of sensorineural hearing loss on an inflammatory "autoimmune" background.

KEY WORDS — Behçet's disease, cyclosporine A, hearing loss.

Behçet's disease is a systemic disorder that is considered now to be an autoimmune disease with a genetic basis.[1-3] Basically, it is an inflammatory disorder involving small blood vessels, particularly venules. Although originally described as a disease manifested by aphthous stomatitis, genital ulcers, and visual disturbances (the classic triad), it soon became evident that many other organs may be affected as a result of the generalized vasculitis. The clinical manifestations are divided into major criteria (oral ulcers, eye lesions, genital ulcerations, and skin lesions) and minor criteria (arthritis, gastrointestinal lesions, epididymitis, thrombophlebitis, and central nervous system involvement).[3]

Since the underlying lesion is vasculitis, it is conceivable that this process may involve also the inner ear, causing hearing loss and vertigo. However, cochlear and vestibular deficits in Behçet patients were described for the first time only in 1980.[4] Some degree of hearing loss was evident in more than 50% of the patients, particularly in those with long duration of the disease. In 1982, two more studies, one from Japan[5] and the other from France,[6] corroborated the finding of a high prevalence of sensorineural hearing loss among Behçet patients. However, these studies lacked a statistical evaluation of the findings.

No therapy has been proven uniformly effective, and the management of Behçet patients requires cooperation among different specialties.[2] Traditionally, the most important drugs are the corticosteroids and cytotoxic drugs, particularly chlorambucil (Leukeran).[2]

Recently, the influence of cyclosporine A (CyA) on the course and acute exacerbation of Behçet's disease has been tested.[7,8] This drug was found to have an unexpected influence on the immune response, acting as an immunomodulator rather than an immunosuppressor.[9] The aims of the present study were 1) to determine the frequency, degree, and type of hearing loss in Behçet patients in comparison with a control group (normal subjects) and 2) to assess the influence of CyA on the cochlear function of Behçet patients.

MATERIALS AND METHODS

In our institution, a long-term multidisciplinary masked study is being conducted, aimed at comparing the efficacy of the conventional therapy (steroids and cytotoxic drugs) with that of CyA in Behçet's disease.[8]

Teams of ophthalmologists, internists, neurologists, otolaryngologists, audiologists, and dentists are involved in this study. Behçet patients having the classic triad of manifestations — ocular, oral, and genital — were randomly assigned to conventional or CyA treatment. Most of these patients demonstrated involvement of additional organs. However, only ocular, oral, and genital involvements were taken into consideration as inclusion criteria for the study.

The ophthalmologists who followed up the patients recorded their findings without knowledge of the assigned treatment. Nonblinded internists who randomized the mode of treatment had access to all the records, monitored the systemic manifestations and the possible side effects, and modified the dose of the medication according to the clinical and laboratory data.

Patients assigned to CyA therapy received a single daily dose of 10 mg/kg, rapidly tapered to 5 mg/kg per day. Patients assigned to conventional thera-

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TABLE 1. CLINICAL MANIFESTATIONS AND MODE OF TREATMENT IN 35 PATIENTS WITH BEHÇET'S DISEASE

	Clinical Manifestations								
Case	*Oral*	*Genital*	*Ocular*	*Skin*	*Joints*	*Vascular*	*Neurologic*	*Hearing Loss**	*Treatment*
1	+	+	+	+	+	−	−	+†	CyA
2	+	+	+	+	+	−	−	+†	CyA
3	+	+	+	+	−	−	−	+†	CyA
4	+	+	+	+	−	−	−	+	CyA
5	+	+	+	+	+	−	+	+	CyA
6	+	+	+	+	+	−	−	+	CyA
7	+	+	+	+	+	−	−	+	CyA
8	+	+	+	−	−	+	−	+	CyA
9	+	+	+	−	−	−	−	+	CyA
10	+	+	+	+	−	−	−	−	CyA
11	+	+	+	−	−	−	−	+	S, then CyA
12	+	+	+	−	−	−	−	+	CyA
13	+	+	+	−	−	−	−	+	S, then CyA
14	+	+	+	+	+	+	+	+†	CyA
15	+	+	+	+	+	−	−	−	CyA
16	+	+	+	+	−	+	+	+	CyA
17	+	+	+	+	+	−	−	+	S
18	+	+	+	−	+	−	−	+	S
19	+	+	+	−	−	−	−	+	S
20	+	+	+	+	+	−	−	+	L, then S
21	+	+	+	+	−	−	−	+	L
22	+	+	+	−	+	−	−	+	CyA
23	+	+	+	+	+	−	−	−	S
24	+	+	+	+	−	−	−	+	S
25	+	+	+	+	−	−	−	+†	CyA
26	+	+	+	+	+	+	−	−	L
27	+	+	+	−	−	−	−	+	S, then CyA
28	+	+	+	+	+	−	−	−	CyA
29	+	+	+	−	+	+	−	−	S
30	+	+	+	−	+	+	−	+	L, then S
31	+	+	+	+	−	+	−	+	L, then S
32	+	+	+	+	−	−	−	−	S
33	+	+	+	+	−	−	−	+	S
34	+	+	+	+	+	−	−	+	S
35	+	+	+	−	+	−	−	+	S

CyA — cyclosporine A, S — steroids, L — Leukeran.

*More than 25 dB hearing level at some or all frequencies.

†Hearing improved.

py were started on a regimen of prednisone 1.0 to 1.5 mg/kg per day or chlorambucil (Leukeran) 0.1 to 0.2 mg/kg per day, with the dose lowered according to the patients' general condition and disease response. Each mode of treatment was continued for a long time (months or years), unless it was changed because of deterioration in the patient's condition (see below).

Thirty-five Behçet patients (26 men and 9 women) were examined in the otolaryngology clinic before entering the study and were regularly followed up for a duration of at least a year. Their mean age was 34.2 years (SD, 9.4; range, 17 to 56 years). Twenty of the 35 patients were randomized to CyA treatment and 15 to conventional therapy.

In three patients who were assigned initially to conventional therapy the eye condition deteriorated so much that a decision was made to unmask them and shift them to CyA therapy. This resulted in the stabilization of the eye condition. (These patients are included in the CyA group.)

In order to evaluate the possible adverse effects of CyA on the inner ear, 12 patients (6 men and 6 women) suffering from unrelated autoimmune eye disease (uveitis) treated with CyA[9] were examined and followed up similarly to the group of Behçet patients. The mean age in this group was 26±13.6 years (range, 10 to 57 years).

As a control group, 35 healthy volunteers, matching the Behçet patients in age and sex ratio, were also examined and followed up.

The audiologic evaluation included 1) behavioral hearing tests (pure tone audiogram including frequencies of 10 and 12 kHz, speech reception threshold, and speech discrimination score), 2) impedance audiometry (tympanometry and acoustic reflex), and 3) recording of auditory brain stem evoked response.

RESULTS

Table 1 shows the various clinical manifestations

TABLE 2. PURE TONE THRESHOLDS OF BEHÇET PATIENTS AND NORMAL SUBJECTS

	0.25 kHz	*0.5 kHz*	*1 kHz*	*2 kHz*	*4 kHz*	*8 kHz*	*10 kHz*	*12 kHz*
Behçet patients (N = 35)								
Mean (dB hearing level)	23.1	21.0	18.8	14.3	19.2	21.0	34.0	41.4
SD	14.6	16.0	18.0	19.9	19.5	19.0	24.5	25.9
Normal subjects (N = 35)								
Mean (dB hearing level)	12.4	11.1	9.3	7.3	6.7	8.2	18.4	29.5
SD	5.3	3.4	4.7	5.2	5.3	5.2	8.6	9.2
t test ($p<$)	.001	.001	.002	.025	.001	.001	.003	.005

as observed in the 35 patients suffering from Behçet's disease. All of them demonstrated oral, genital, and ocular involvement (criteria for inclusion in the study). Many showed also skin, joint, and vascular problems. Only 3 patients (8.5%) presented neurologic signs.

Twenty-eight patients (80%) showed some degree of hearing loss in the pure tone audiogram at some or all of the frequencies tested (more than 25 dB hearing level). This hearing loss was unilateral in 8 patients and bilateral in 20. Only 7 of the 35 Behçet patients (20%) had normal cochlear function (within 25-dB range).

Table 2 and Fig 1 show the averaged pure tone thresholds of the Behçet and the normal subject groups in the various frequencies (mean and SD). There is no clear typical pattern of hearing loss for Behçet patients, and it was found that any shape of audiogram is compatible with the disease.

In each frequency, the mean and the SD were found to be higher in the Behçet group than in the normal subjects. The difference between the two averaged audiometric curves (Behçet versus control) was tested by ANOVA with repeated measurements and was found to be statistically significant ($p<.02$). A significant difference was found also at each tested frequency (Table 2). No significant difference was found regarding the speech reception thresholds, speech discrimination scores, or impedance audiometry between the Behçet patients and the normal subjects. In addition, no significant difference was found regarding the mean hearing level between the uveitis group and the control group. In the follow-up period, no significant changes in the pure tone thresholds were found among the 15 Behçet patients treated with conventional therapy or among the 12 uveitis patients who were treated with CyA. On the other hand, among the 20 Behçet patients who received CyA, 5 patients (25%) showed a significant improvement of hearing (more than 15 dB) in several frequencies. Figures 2 through 4 show the audiograms of 3 such patients. This difference between the conventional treatment and

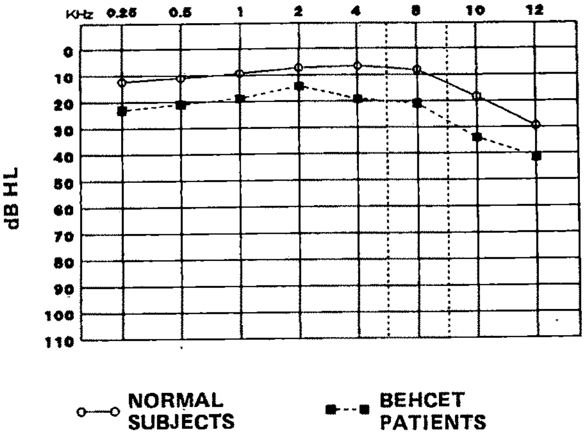

Fig 1. Averaged pure tone audiogram of Behçet patients and normal subject group.

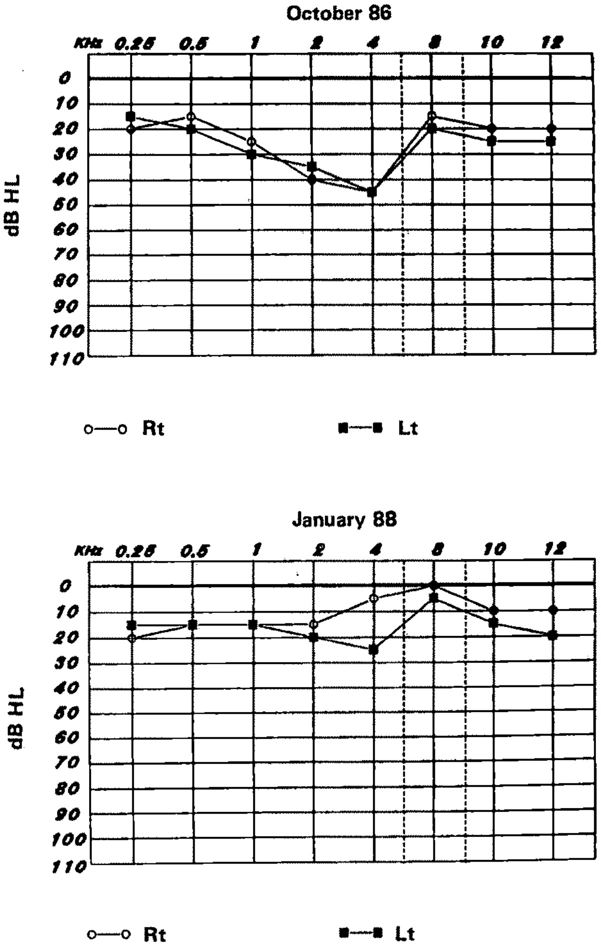

Fig 2. Two audiograms of 39-year-old Behçet patient treated with cyclosporine A. First audiogram was taken just before treatment started, and second while patient was still on maintenance regimen. Note marked improvement of hearing threshold at middle frequencies, particularly in right ear.

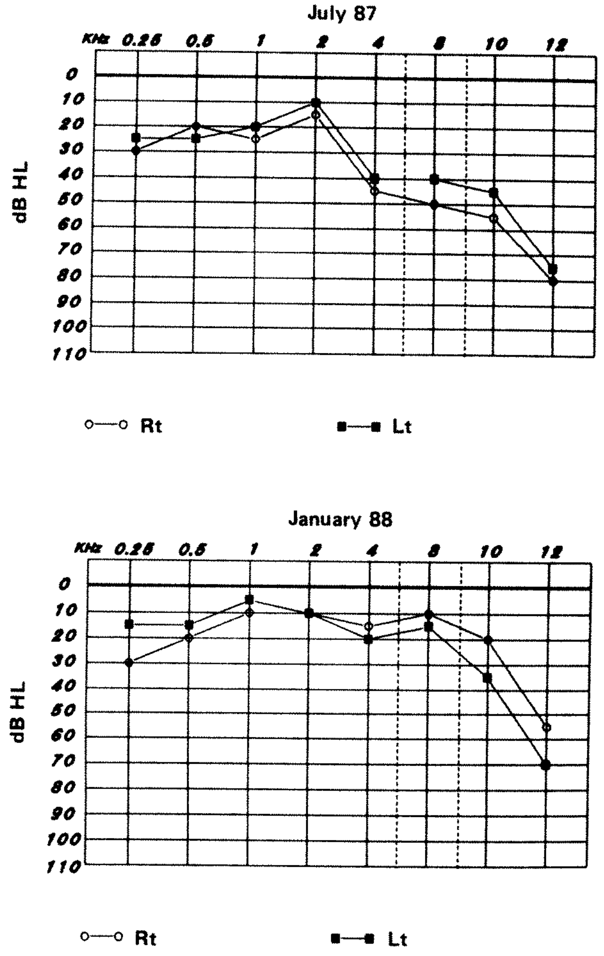

Fig 3. Two audiograms of 56-year-old Behçet patient treated with cyclosporine A. First audiogram was taken just before treatment started, and second while patient was still on maintenance regimen. Note marked improvement in hearing in high frequencies, especially in right ear.

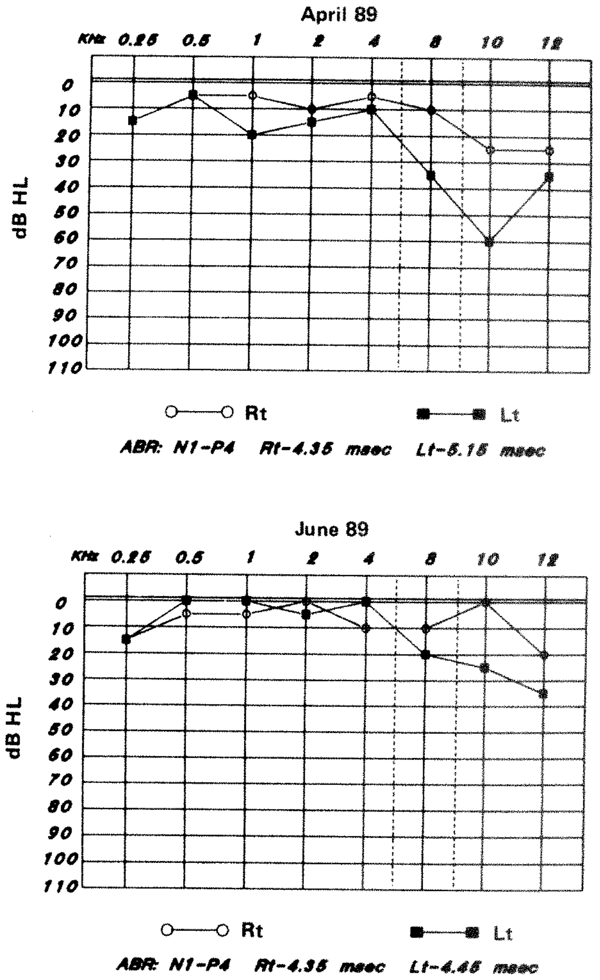

Fig 4. Two audiograms of 16-year-old Behçet patient treated with cyclosporine A. Note marked improvement in high frequencies accompanied by shortening of brain stem transmission time (N1-P4) in auditory brain stem evoked response recordings.

the CyA treatment groups was statistically significant (Fisher's exact test, $p < .05$).

None of the Behçet patients in either therapy group demonstrated any deterioration of hearing during the follow-up period. All the auditory brain stem evoked response recordings from the uveitis patients were within normal range. In contrast, one of the Behçet patients under CyA treatment who suffered from unilateral sensorineural hearing loss produced also an abnormal recording in the affected ear (prolonged brain stem transmission time). Interestingly enough, following the CyA treatment, a marked improvement in the hearing was accompanied by normalization of the evoked response recording (Fig 4).

DISCUSSION

Behçet's disease is a chronic systemic vasculitis affecting many organs. When the eyes are involved there is a rapid deterioration of vision leading to blindness. Recently, involvement of the inner ear has also been reported.[4-6] The present study is the first in the literature in which it is proven statistically that Behçet patients (who are usually young; mean age in our study, 34.2 years) indeed suffer from significant hearing deficits. Thus, similar to other autoimmune diseases (such as periarteritis nodosa and temporal arteritis),[10,11] Behçet's disease, in which the basic lesion is vasculitis, also affects the inner ear, causing hearing loss and vertigo.

With regard to the eye manifestations and prevention of blindness, the conventional therapy with chlorambucil and steroids has been disappointing.[12] Therefore the masked, randomized clinical trial with CyA was suggested and is being conducted in our hospital.[8]

Treatment with CyA has been more effective than conventional therapy in controlling ocular inflammation and in preservation of vision.[8] However, these clearly beneficial effects were not observed when the other systemic manifestations were analyzed. It is interesting, therefore, that 5 of 20 patients with Behçet's disease showed a marked improvement of their auditory function when taking CyA. Although the group of Behçet patients receiving conventional therapy in this study is smaller, none of them has shown improvement of hearing during the follow-up. This difference between the two modes of treatment was found to be statistically significant (Fisher's exact test, $p < .05$). Thus, CyA treatment may be beneficial for the auditory function, leading to the reversal of the hearing loss occurring during the disease process.

Cyclosporine A was originally discovered as a metabolite of soil fungi in a search for new antibiotics.[13] Unexpectedly, it was found that CyA has an extensive influence on the immune response.[14] In experimental animals, CyA prolongs graft survival and prevents the induction of experimental allergic encephalitis and other autoimmune inflammatory disorders.[15,16] In human subjects the outstanding effects of CyA in preventing the rejection of kidney and heart transplants is well established. The effect of CyA in spontaneous autoimmune diseases in animal models and in humans is still under investigation.[17]

All the patients receiving CyA complained of one or more side effects, notably paresthesia, gingival hypertrophy, hypertrichosis, fatigue, and gastrointestinal discomfort. The most serious side effects of CyA are nephrotoxicity and hepatotoxicity. These can be minimized, as in the present study, by tight control of the serum creatinine and liver function tests and avoidance of a high serum level of CyA for prolonged periods.[18] The addition of steroids to CyA can be beneficial also in allowing reductions in the dose of CyA, thereby reducing the risk of nephrotoxicity.

The present study showed that CyA, in the clinical dosage used, does not have a cochlear ototoxic effect, since no patient in the uveitis group showed any sign of hearing deterioration during the follow-up period.

The fact that hearing improvement was demonstrated in five Behçet patients treated with CyA is very encouraging. Although the number is too small for us to draw a final conclusion, it is suggested that CyA may be used as an alternative mode of treatment either alone or in combination with other drugs for the treatment of "autoimmune" inflammatory disorders[19] involving the inner ear and causing sensorineural hearing loss and/or vertigo.

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MIDDLE EAR PRESSURES OF CHILDREN WITH OTITIS MEDIA WITH EFFUSION

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Middle ear (ME) pressures were measured in 30 children with chronic otitis media with effusion (OME) transtubally with the use of a catheter pressure transducer (Mikro-tip, PC-330F). They were found to range from 40 to -185 mm H_2O, the average being mildly negative (-54.33 ± 59.04 mm H_2O). About two thirds of these children had pulsating changes of ME pressure; the range of the pressure change was between 10 and 50 mm H_2O. The ME pressure tended to be lower in ears with serous effusion than in those with mucoid effusion, but there was no significant difference between them.

KEY WORDS — middle ear pressure, otitis media with effusion.

INTRODUCTION

Middle ear (ME) pressure of ears with otitis media with effusion (OME) has been known to be negative in most cases because of the fact that the eardrums of these patients usually retract. Although the origin of this negative ME pressure of OME patients has been explained by the "hydrops ex vacuo" theory, several experimental studies[1-3] have failed to produce a negative ME pressure low enough to induce transudate[4] when only the transtubal ventilation of the ME was impaired. On the other hand, some other experimental studies have shown that when there is fluid in the ME cavity, a negative ME pressure can be induced by the clearance of the ME fluid via the clearance function of the eustachian tube (ET).[5,6] Pathogenesis of the negative ME pressure among OME patients is, therefore, still controversial, and precise information about ME pressure in OME patients would give us an important clue to solve this issue. However, to our knowledge, precise ME pressures of a considerable number of OME patients measured with a consistent method have never yet been reported.

We have used a catheter pressure transducer to directly measure the ME pressure by introducing it to the ME through the ET, and its reliability has already been reported by the simultaneous recordings of the ME pressures with this transducer and the tympanogram on four normal ears during general anesthesia.[7] In this report, we show the results of measurements of ME pressure in 30 children with OME.

MATERIALS AND METHODS

Participants in this study were 25 children (3 to 8 years of age) with 30 ears with chronic OME who underwent myringotomy or ventilation tube insertion and/or adenoidectomy under general anesthesia.

To avoid an increase of ME pressure, general anesthesia was performed with only 30% oxygen and halothane or enflurane without nitrous oxide. A fine catheter pressure transducer (Mikro-tip, PC-330F, Miller Instruments), which had been kept in 37°C sterile saline for 30 minutes before use for adaptation of the pressure sensor at the tip of the transducer to the body temperature, was inserted into the ME through the ET, guided by an inflation catheter. That the transducer was correctly introduced into the ME was confirmed by the increase of ME pressure with a light compression of the tympanic membrane. The ME pressure was measured for 5 to 10 minutes to confirm that there was no pressure change due to air leakage through the ET. Finally, it was confirmed that the ME pressure returned to atmospheric pressure by myringotomy and suction of ME effusion. The correlation between ME pressure and the character of the ME effusion of each ear was also examined.

RESULTS

Results are summarized in the Table. The ME pressure ranged from 40 mm H_2O to −185 mm H_2O among the 30 ears examined; 5 ears showed positive pressure, 2 ears showed atmospheric pressure, and the remaining 23 showed negative pressure. Overall, the ME pressure of the OME children was found to be mildly negative at −54.33 ± 59.04 mm H_2O on average (Fig 1).

About two thirds of the patients (21 patients) had

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MIDDLE EAR PRESSURES OF CHILDREN WITH OTITIS MEDIA WITH EFFUSION

Case	*Age (yr)*	*Sex*	*Side*	*Effusion*	*Middle Ear Pressure (mm H2O)*
1	5	F	L	Mucoid	-80
2	6	M	L	Serous	-50
3	5	M	R	Mucoid	40
4	5	M	L	Mucoid	-110
5	6	M	R	Mucoid	-45
			L	Mucoid	10
6	6	M	L	None	-55
7	7	F	L	None	0
8	7	M	R	Mucoid	30
9	6	F	R	Mucoid	-20
10	6	M	R	Mucoid	-60
			L	Mucoid	-80
11	5	M	R	Mucoid	-30
			L	Mucoid	0
12	5	F	R	Mucoid	40
13	5	M	L	Serous	-130
14	6	F	L	Serous	-20
15	7	M	R	Serous	-170
			L	Serous	-110
16	6	F	L	Mucoid	-85
17	5	M	L	Serous	5
18	6	M	L	None	-30
19	8	M	R	Mucoid	-20
20	5	F	L	Mucoid	-55
21	6	M	L	Mucoid	-70
22	3	M	L	Mucoid	-60
23	4	F	R	Mucoid	-30
24	6	M	L	Mucoid	-150
25	6	F	R	None	-185
			L	Mucoid	-110

pulsating changes in ME pressure; the degree of the pressure change ranged from 10 to 50 mm H_2O. The frequency of the pulsation was identical to that of the cardiac pulsation of each patient, and the waveform of the ME pressure was very similar to that of arterial pressure (Fig 2). All these pulsating changes of ME pressure disappeared after myringotomy and suction of the ME effusion.

The ME pressures of ears with mucoid effusion (20 ears) tended to be higher than those of ears with serous effusion (6 ears), but there was no significant difference between them (see Table and Fig 2).

COMMENTS

From our results, OME children were found to have a slightly negative ME pressure of -54.33 ± 59.04 mm H_2O on average, and none had negative pressure lower than -200 mm H_2O. These values are similar to those measured through the eardrum by Kawabata et al[8] (-170 to 70 mm H_2O), and are not contradictory to the ones calculated by Sade[9] from manometric values and ME mastoid volumes. Although it is not necessarily appropriate to speculate on the pathogenesis of OME or the origin of the negative ME pressure in OME only from these data obtained from ears with chronic OME, these values do not appear to be compatible with the pressure necessary to induce ME transudate in humans according to Flisberg et al[4] (-20 mm Hg or -272 mm H_2O). Rather, they are similar to those observed when only the ventilatory function of the ET is impaired,[1,2] or those observed when ME fluid is excreted via the ET by the ciliary function of the ET.[5,6] There seems to be some possibility that ME effusion in OME children might be other than the transudate induced by negative ME pressure.

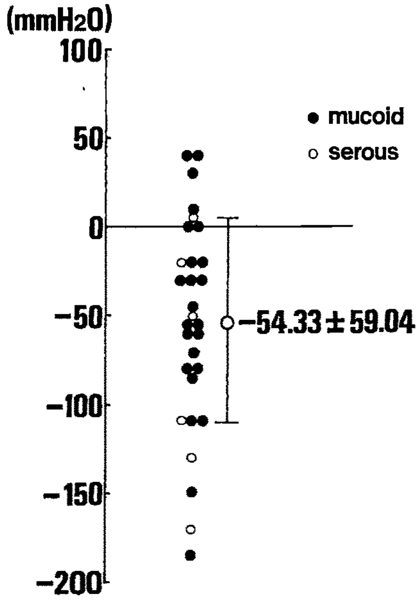

Fig 1. Middle ear pressures of 30 children with otitis media with effusion.

It is also important to note that the negative ME pressures seen in most OME children cannot be released, because active tubal ventilatory function, especially with negative ME pressure, is impaired in 97% of OME children.[10] The ME effusion may be constantly drained via the ET if negative ME pressure is efficiently released transtubally, because ME effusion was reported to be drained within a short time only with myringotomy.[9,11] In light of these findings, the negative ME pressure in most OME children seems to be one of the important factors causing the "deadlocked" pathophysiologic condition of the ME and ET in OME patients, in whom negative pressure and fluid coexist and the fluid cannot be drained anymore because of the negative ME pressure.

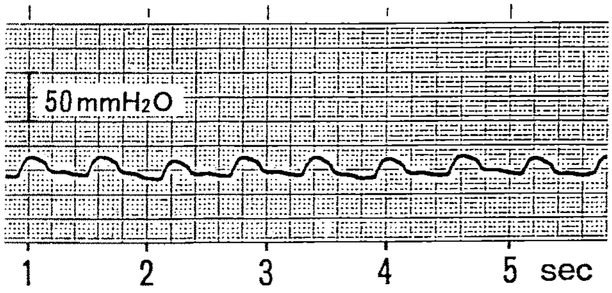

Fig 2. (Case 2) Pulsatile change of middle ear pressure.

Pulsating changes of ME pressure with considerably wide ranges were seen in almost two thirds of the OME children examined. They appear to be brought on by pulsation of an adjacent great artery — that is, the internal carotid artery (ICA) at the bony portion of the ET — because the frequency was identical to the cardiac pulsation, and because the waveform was very similar to that of arterial pulsation. Moreover, there is no other great artery closer to the ME and ET than the ICA. The carotid canal at the bony portion of the ET was reported to have a dehiscence in 2% and to be wafer-thin in 22.2% of humans.[12] Generally speaking, pressure tends to be transmitted more easily in fluid than in air. This may be why so many OME children had pulsating changes of their ME pressure; in other words, when the ME is filled with fluid, pulsation of the ICA may be transmitted to the ME cavity through the bony wall even if it is intact.

The ME pressure tended to be lower in ears with serous effusion than in those with mucoid effusion, but there was no significant difference between them. If the negative ME pressures are created by the transtubal drainage of the ME effusion, those in the ears with serous effusion might be higher than those in ears with viscous mucoid effusion because fluid with a lower viscosity is excreted more easily by ciliary transportation of the ET than that with a higher viscosity.[13] For the final conclusion of this issue, however, more accumulation of data seems to be necessary.

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THE DEAFNESS RESEARCH FOUNDATION
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The Deafness Research Foundation's Otological Research Fellowship will be sponsored by a department of otolaryngology conducting otological research. Where a unique opportunity exists in a related discipline, the fellowship may be conducted in that discipline while maintaining liaison with the department of otolaryngology. The fellowship would be scheduled as a one-year block of time at the end of the third year of medical school, thus requiring a one-year leave of absence from the medical school curriculum. The fellowship would be funded in the amount of $10,000, plus up to $3,500 for animals and consumable supplies. Applications for 1992 funding must be received by November 15, 1991. For more information, please contact Walter A. Petryshyn, MD, Medical Director, The Deafness Research Foundation, 9 East 38th Street, New York, NY 10016; (212) 684-6556.

Ann Otol Rhinol Laryngol 100:1991

POSTURAL COMPENSATION IN CHILDREN WITH CONGENITAL OR EARLY ACQUIRED BILATERAL VESTIBULAR LOSS

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The relative roles of different receptor systems in compensating for vestibular loss were studied in 18 children (12 to 16 years of age) with congenital or early acquired bilateral vestibular loss (BVL) and impaired hearing, and compared to that in 33 normal children (9 to 16 years of age). Postural stability was studied with posturography evaluating the velocity of anterior-posterior body sway. With closed eyes the *increase* of sway velocity did not differ between the groups, either with or without simultaneous proprioceptive disturbances when the subjects were standing on a bare surface. Body sway velocities were found to increase more in subjects with a BVL than in normal children when subjects were standing on foam rubber. When proprioceptive cues were disturbed, body sway velocities increased in both groups, but significantly more in children with BVL when subjects stood on foam rubber. This occurred both with and without open eyes.

KEY WORDS — children, compensation, foot, mechanoreceptors, postural control, proprioception, visual control.

INTRODUCTION

It is assumed that information from the pressor receptors of the soles, and proprioception together with vestibular information, provide the necessary input for posture control during stance.[1,2] These plus visual information assist control as they provide information about orientation and adjust the weight of each receptive system in the control process.[3] Usually a lesion to one of the sensory systems is compensated for, but lesions to two systems will leave the subject with less than full compensation. Even so, the roles of the different receptor systems in postural control have not been fully elucidated.

Vestibular deficits are common in children with congenital or early acquired profound hearing loss.[4,5] Such children are considered to stand and walk later than other children.[6,7] Children with impaired hearing are encouraged to take part in physical education and activities with demands on motor development, and as teenagers there are no evident postural disturbances in everyday life compared to normal children.[7,8] Thus, a bilateral defect in vestibular function since early childhood can be compensated for in everyday activities.

So far, it has not been documented what strategy subjects with early acquired bilateral vestibular loss (BVL) will adopt to compensate for such a deficit. In the present work postural control was studied in children with BVL during controlled disturbances to the different receptor systems engaged in detecting postural information. The aim was to investigate the relative importance of the different receptor systems in maintaining postural control after compensation for early acquired BVL.

SUBJECTS

Eighteen children with congenital or early acquired BVL, 12 to 16 years of age (mean, 13.8 years), were recruited from the public school system for children with impaired hearing in Lund and Örebro, Sweden. Apart from the hearing and vestibular losses they had no known physical, neurologic, or mental deficits. All children in this group had reductions of their hearing thresholds greater than 90 dB in both ears. In all cases the hearing loss was acquired before or during the first 2 years of life. Eight children had a confirmed hereditary hearing loss (6 with Usher's syndrome types 1 and 2 unclassified) and 10 had lost their hearing as a result of meningitis. In none of the children could vestibular nystagmus be elicited by a velocity step rotation test (150°/s).[9] Peak velocity and accuracy of voluntary saccades[10] were within normal range in all children with BVL. Visual acuity and contrast sensitivity were normal in the children with Usher's syndrome included in the study except for some narrowing of the visual field. The control group consisted of 33 normal children 9 to 16 years of age (mean age, 13.2 years) without any physical or neurologic deficit and without known ear diseases other than occasional acute secretory or purulent otitis media in infancy.

METHODS

Postural control was evaluated with posturography. The forces actuated by the feet were recorded with a force platform equipped with strain gauges.[11] During the recordings the subjects stood erect, with the arms crossed over the chest and with the feet together forming a forward open angle of

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TABLE 1. *T* TEST (SEPARATE GROUPS)

	Normal Children		*Children With BVL*	
	Open Eyes	*Closed Eyes*	*Open Eyes*	*Closed Eyes*
Solid versus foam rubber surface				
No vibration	$p<.001$	$p<.001$	$p<.001$	$p<.001$
Vibration 80 Hz	NS	$p<.01$	$p<.001$	$p<.001$
	Normal Children		*Children With BVL*	
	Solid	*Foam*	*Solid*	*Foam*
Open versus closed eyes				
No vibration	NS	$p<.01$	NS	$p<.01$
Vibration 80 Hz	$p<.001$	$p<.001$	$p<.001$	$p<.001$

BVL — bilateral vestibular loss, NS — not significant.

30°. During the tests the neck was restricted by an orthopedic collar to reduce active head movements. In each of the test conditions the body posture was perturbed by vibratory stimulation of the calf muscles (vibration-induced body sway).[12,13] The vibrators were attached with elastic straps to the belly of the gastrocnemius muscle on each leg. The vibratory stimulus had a constant amplitude of 0.4 mm (peak to peak) and was given at frequencies of 20, 40, 60, 80, and 100 Hz according to a pseudorandom pattern.[12] The vibrators were driven by a programmable power supply controlled by a microcomputer (HP75). Measurements were made either with eyes open (visual control condition) or with eyes closed (nonvisual condition). Furthermore, recordings were made with subjects standing directly on the solid surface of the force platform and subsequently on a 5-cm-thick mat of foam rubber (0.31 g/cm^3). The latter condition was designed to eliminate or reduce pressor receptor information from the feet.[14] The recorded signal from the platform, measuring the force distribution on the platform surface, was digitized at 33 Hz and fed into an HP 9000 (300 series) computer.[15] The computer permitted analysis of the velocity of body sway as well as amplitude in the anterior-posterior and the lateral planes. The variables were calculated separately for each different period of vibration as well as for the stimulation-free periods.[11]

ANALYSIS

The mean absolute body sway velocity in the anterior-posterior and lateral planes was used in evaluation of postural control. Evaluations were made in subjects standing either on the solid surface or on a foam rubber mat on top of the platform, with eyes open or closed, with and without vibration. Comparisons of the effect of different stimulus conditions were made within as well as between the groups of normal and vestibular-deprived children (Table 1).

The importance of information from the different receptor systems was evaluated by calculating the change in body sway velocity caused by introduction of a disturbance to the sensory systems. When differences were calculated they were denoted "delta values," or when quotients were calculated, "Romberg quotients." For visual cues, delta values were calculated as the difference between body sway velocities with eyes closed and eyes open (closed minus open); for proprioceptive cues, the difference between body sway velocities during simultaneous vibration of the calf muscles (80 Hz)[10] and during no vibration (80 Hz minus 0 Hz); for pressor receptor function, the difference between body sway velocities when subjects were standing on foam rubber and when they were standing on the solid surface of the force platform (foam rubber minus solid surface) (Table 2). Romberg quotients were formed by the quotients between body sway (eyes closed divided by eyes open, vibration of 80 Hz divided by no vibration, and foam rubber surface divided by solid surface).[16]

The Kolmogorov-Smirnov test was used to evaluate the normality of samples, and comparisons were subsequently made by using Student's *t* test or a Mann-Whitney *U* test for paired or unpaired samples. A difference of $p<.05$ was considered significant.

RESULTS

Children With Normal Inner Ear Function. With eyes closed the body sway velocity was significantly greater than with open eyes if the subjects were standing on foam rubber or if there was simultaneous vibration of the calf muscles. When subjects were standing on the solid surface of the platform

TABLE 2. *T* TEST (COMPARING GROUPS)

	Open Eyes		*Closed Eyes*	
	Solid	*Foam*	*Solid*	*Foam*
Normal children compared to children with BVL				
No vibration	NS	NS	NS	$p<.01$
Vibration 80 Hz	NS	$p<.001$	$p<.01$	$p<.001$

BVL — bilateral vestibular loss, NS — not significant.

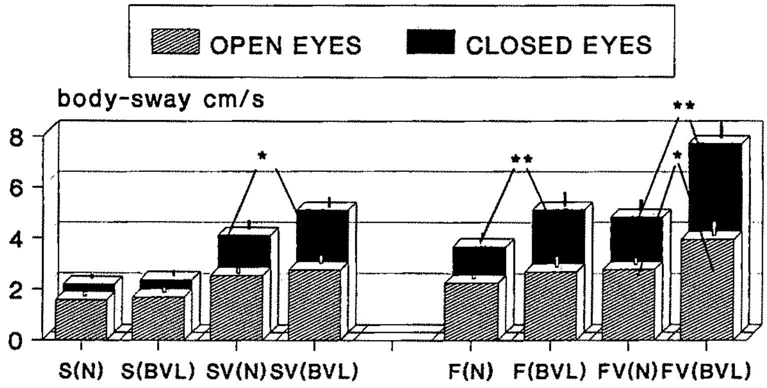

Fig 1. Body sway velocity (mean and SEM) in normal children (N) and children with bilateral vestibular loss (BVL) with and without disturbance of vision. Outcome of four different test conditions is given, ie, standing on solid surface (S) or standing on foam rubber surface (F) with (V) or without vibration. * — p<.01, ** — p<.001.

	S(N)	S(BVL)	SV(N)	SV(BVL)	F(N)	F(BVL)	FV(N)	FV(BVL)
CLOSED EYES	1,89	2,07	3,82	4,81	3,36	4,81	4,52	7,42
SEM	0,12	0,22	0,33	0,48	0,24	0,61	0,27	0,89
OPEN EYES	1,58	1,69	2,54	2,76	2,24	2,68	2,77	3,96
SEM	0,13	0,18	0,19	0,24	0,17	0,34	0,22	0,43

without any further stimulus, there was no significant difference between recordings with closed and open eyes (Table 1 and Fig 1).

Standing on a foam rubber surface, normal children exhibited a significantly higher body sway velocity compared with standing on a solid surface in all test conditions with the exception of when the subjects were exposed to vibration with open eyes (Table 1 and Fig 2).

Children With Bilateral Vestibular Loss. Results of the posturographic measurements are given in Table 1. With eyes closed without any further disturbance, there was no significant increase in body sway (Fig 1). With eyes closed and simultaneous 80-Hz vibration, however, the body sway velocity increased significantly in all test conditions (solid surface as well as foam rubber surface) (Fig 3).

Standing on a foam rubber surface, children with BVL always demonstrated a significantly higher body sway velocity than when standing on a solid surface. This was true regardless of whether recordings were made with eyes open or closed, or with or without simultaneous vibration (Fig 2).

Comparison. Results of the measurements are given in Table 2 (comparing controls and children with BVL). With open eyes there was no difference between normals and children with BVL when they were standing on a solid surface or on foam rubber without simultaneous vibration (Fig 1). Neither were there any differences in body sway velocity between the groups if the subjects were exposed to vibration simultaneously. However, when the children were standing on foam rubber and exposed to simultaneous vibration of the calf muscles, children with BVL demonstrated a significantly higher body sway velocity than did normal children (Table 2 and Fig 1).

With closed eyes there was no difference between normal children and children with BVL when they were standing on a solid surface without further stimulation (Fig 2). When subjects were exposed to vibration with closed eyes, the children with BVL

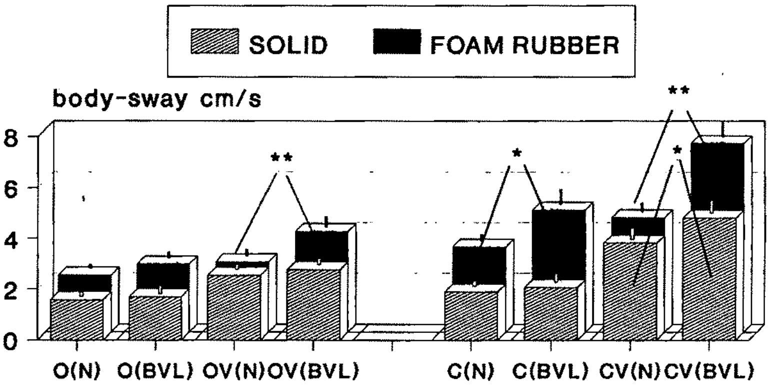

Fig 2. Body sway velocity (mean and SEM) in normal children (N) and children with bilateral vestibular loss (BVL) with and without disturbance of proprioception. Outcome of four different test conditions is given, ie, with open eyes (O) or with closed eyes (C) while standing on solid surface or on foam rubber surface. V — vibration, * — p<.01, ** — p<.001.

	O(N)	O(BVL)	OV(N)	OV(BVL)	C(N)	C(BVL)	CV(N)	CV(BVL)
FOAM RUBBER	2,24	2,68	2,77	3,96	3,36	4,81	4,52	7,42
SEM	0,17	0,34	0,22	0,43	0,24	0,61	0,27	0,78
SOLID	1,58	1,69	2,54	2,76	1,89	2,07	3,82	4,81
SEM	0,13	0,18	0,19	0,24	0,12	0,22	0,33	0,48

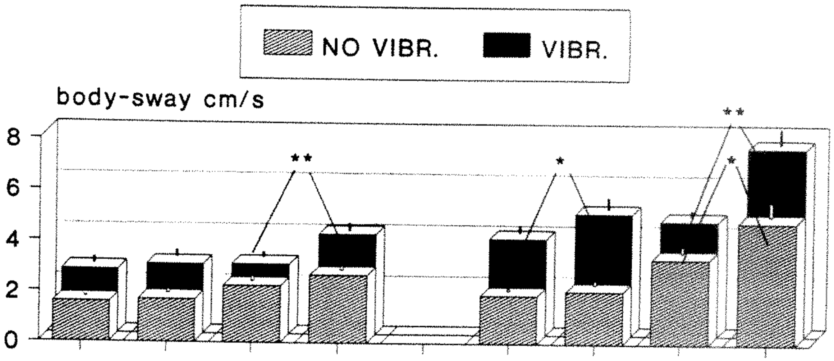

Fig 3. Body sway velocity (mean and SEM) in normal children (N) and children with bilateral vestibular loss (BVL) with and without disturbance of pressor receptor information from soles. Outcome of four different test conditions is given, ie, with open eyes (O) or with closed eyes (C) while standing on solid surface or on foam rubber surface (F). * — p<.01, ** — p<.001.

	O(N)	O(BVL)	OF(N)	OF(BVL)	C(N)	C(BVL)	CF(N)	CF(BVL)
VIBR.	2,54	2,76	2,77	3,96	3,82	4,81	4,52	7,42
SEM	0,19	0,24	0,22	0,43	0,33	0,48	0,27	0,78
NO VIBR.	1,58	1,69	2,24	2,68	1,89	2,07	3,36	4,81
SEM	0,13	0,18	0,17	0,34	0,12	0,22	0,24	0,61

had significantly higher body sway velocities compared to normal children (Fig 2). Significant differences were also observed with closed eyes standing on foam rubber and standing on foam rubber with simultaneous vibration (Table 2 and Fig 2).

Relative Importance of Different Receptor Systems. The relative importance of the different receptor systems was tested by comparing the increase in body sway velocity (ie, delta values and Romberg quotients) between normal children and children with BVL (see Methods) (Table 3). The outcome of statistical comparison of Romberg quotients did not differ in general from the results found when comparing delta values. Therefore, only the results in delta values will be discussed.

As regards vision, the increase of body sway velocity caused by closing the eyes was of about equal magnitude in normal children and BVL children if they were standing on solid or foam rubber surfaces (solid or foam in Fig 2) or with or without simultaneous bilateral proprioceptive disturbance to the gastrocnemius muscles (vibration or no vibration in Fig 3).

As regards proprioception, vibration of the calf muscles increased body sway velocity to the same magnitude in normal children and children with BVL when standing on a solid surface, and whether they had open or closed eyes, but in BVL children it was increased more than in normal children when standing on foam rubber (Fig 2).

As regards pressor reception, standing on foam rubber increased body sway velocities in children with BVL more than in normal children in all except a neutral condition (eyes open, no vibration in Fig 3).

DISCUSSION

In the absence of functioning vestibular end-organs the strategy of postural control is redistributed among visual, proprioceptive, and exteroceptive receptors. In the present experimental setup, pressor receptors of the soles and proprioception were found to be of equal importance to or more important than visual feedback in maintaining stability in children with BVL. That finding is in contrast with the postural strategy adopted by adult subjects, who mainly depend on visual cues and who cannot attain as good compensation after bilateral vestibular function loss as children with BVL can.[17] Furthermore, children with BVL can achieve good postural compensation. No difference in body sway velocities was found compared with normal children when standing with open eyes, except when standing on foam rubber. Nor was there any difference with closed eyes if there were no further disturbances. However, if there was simultaneous disturbance of the proprioception or pressor information from the soles, postural control decreased significantly more in children with BVL when standing with closed eyes compared to normal children.

In the present study a BVL was considered to be present when no nystagmus could be elicited by rotation with a velocity step of 150°/s (acceleration, $40°/s^2$). The above criteria do not exclude the possibility of some residual vestibular response to movements in other planes or in otolith function. In fact, some reports point out that in Usher's syndrome the maculae in the utriculi may be intact while the crista shows pronounced degeneration along with the cochlea.[18] However, lesions or maldevelopments affecting the inner ear and causing bilateral severe hearing loss and loss of any vestibular reaction in the horizontal plane generally affect the otolith organs and all semicircular canals as well.[19] Any remaining vestibular function in such an ear would presumably contribute very little to postural control.

The present findings indicate that visual information is of importance for postural control in BVL

TABLE 3. DELTA (*T* TESTS OF DIFFERENCES)

	Open Eyes	*Closed Eyes*
Effect of disturbance on pressor receptors (solid minus foam)		
No vibration	NS	$p<.05$
Vibration 80 Hz	$p<.05$	$p<.05$
	Open Eyes	*Closed Eyes*
Effect of disturbance on proprioception (no vibration minus vibration)		
Solid surface	NS	NS
Foam rubber surface	$p<.05$	$p<.001$
	Solid	*Foam Rubber*
Effect of disturbance on visual system (eyes open minus eyes closed)		
No vibration	NS	NS
Vibration 80 Hz	NS	NS

NS — not significant.

children as well as in normal children. However, when there are no further sensory conflicts, visual information is not necessary for maintaining postural control in children with BVL equal to that of normal children. The effects of a proprioceptive disturbance indicate that proprioceptive cues from the calf muscles contribute to postural control in children with BVL as well as in normal children. This contribution becomes significantly more important for children with BVL in conditions in which there is a disturbance of the pressor receptor function (Table 3). Furthermore, pressor information from the soles can compensate for either visual or proprioceptive disturbances in children with BVL, but not for the two in concert. The significant increase of body sway velocities in children with BVL compared to normal children when standing on foam rubber indicates that pressor receptor contribution is more important to postural control for these children than for normal children.

Thus, the present results demonstrate that children with BVL can maintain a postural stability almost equal to that of normal children by compensating the loss of vestibular function using information from proprioception, vision, and the pressor reports of the soles. However, when exposed to different sensory loading, children with BVL are more affected by disturbances of pressor receptors than are normal children. Hence, the present results seem to indicate that although information from all the different receptor systems can compensate for losses in another system, the information from the pressor receptors of the soles is of significant importance for children with BVL.

Pressor reception from the soles is transduced by the mechanoreceptors of the glabrous skin of the foot. Four different kinds of receptor units have been identified in the glabrous skin of the human foot. Depending on receptive properties they are classified as pacinian corpuscle–like (PC-like), rapid-adapting (RA), slow-adapting I (SA I), and slow-adapting II (SA II).[20] The PC-like and RA receptors quickly adapt to an applied pressure and can be demonstrated to detect velocity and acceleration of changes in indentation of the skin.[21] Receptors that are PC-like can also detect transients in pressure changes and sinusoidal vibration above 64 Hz.[22] The SA I and SA II types of receptors adapt slowly to an applied pressure and hence can detect position and strength of a slow indentation of the skin. The SA I receptors are also able to detect indentation velocity. While the RA and SA I receptors have small receptive fields, SA II and PC-like receptors have receptor fields 5 to 10 times their size.[23] The SA II receptors also detect stretching of the skin — for example, that due to movements of the ankle. These different populations of receptors overlap each other in properties as well as in receptive fields.[21,23] Hence, one should not consider them as separate sensor organs, but consider pressor reception of the soles as one unified function.[24] Recently it was demonstrated that reduction of pressor information from the soles in normal subjects, standing on a solid surface, increased body sway.[25] Although visual cues reduced the effect of disturbed pressure information in this study, postural control was not restored to normal even when subjects stood with open eyes.

The body sway velocity increased with the same magnitude in both groups when standing with closed eyes (Table 2), suggesting that visual contribution is of equal importance in children with BVL as in normal subjects. Such conclusions are in contradiction with some earlier reports,[1,4] but recently Black et al[26] reported findings compatible with ours. These authors found that children with BVL did not differ from normal children when standing on a solid surface with closed eyes. However, they found children with BVL to be more affected than normals when tested with closed eyes on a moving support surface, which in fact also had an effect on pressor reception.

The good postural stability in BVL children standing with closed eyes in a disturbance-free setting might be understood in the light of recent results reported by Haas and Diener.[27] They analyzed the use of anticipatory postural adjustments and suggested that this ability develops in parallel with postural feedback control in children. The ability to anticipate a disturbance of posture must depend either on memory or visual information or both. For example, feed-forward control contributes to postural control when one is walking in daylight, reducing the number of errors demanding fast feedback control. When one is walking in darkness, visual information is lost and the feed-forward control is hampered. Thus, the subject becomes more dependent on feedback control and vestibular function. It seems feasible that children with BVL may benefit from applying anticipatory postural adjustments, ie, feed-forward control, thus reducing the need for vestibular information. However, when one is exposed to an unpredicted perturbation, ie, a situation of mainly feedback control, vision may have less importance. Recently it has been reported that visual information can reduce the effect on vibration-induced perturbations only in the low frequency range, ie, up to about 0.05 Hz.[13,28] Similar findings were reported by Roos et al,[29] who found that adult subjects with a compensated BVL could use visual information only below 0.2 Hz to adjust posture. In the present study the subjects were perturbed with a vibratory stimulus and/or by standing on a foam rubber surface, causing an increase in body sway. It is suggested that the induced body sway might be in the frequency range above that which could be compensated for with vision-dependent feed-forward control. Thus, closing the eyes would have the same effect on postural control in children with BVL and normal children, as was found.

CONCLUSION

By using visual, proprioceptive, and exteroceptive cues, children with congenital or early acquired vestibular loss can compensate for the vestibular deficiency in postural control. The pressor receptors of the feet and the proprioception are of major importance for this postural compensation. Visual cues contribute to reduce body sway in these children, but have a similar effect of the same magnitude in normal children.

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Ann Otol Rhinol Laryngol 100:1991

PERINATAL VERTICAL TRANSMISSION OF HUMAN PAPILLOMAVIRUS AND SUBSEQUENT DEVELOPMENT OF RESPIRATORY TRACT PAPILLOMATOSIS

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This study prospectively examined the potential for human papillomavirus (HPV) to be transmitted vertically to newborns during delivery. Exfoliated cervical cells were extracted from 72 pregnant women during the third trimester and again during labor prior to delivery, and tested for the presence of HPV DNA. These results were compared with HPV DNA specimens from their newborns, who were sampled by exfoliated cells from the oral-pharyngeal cavity and vulva or tissue from the foreskin 24 to 72 hours after delivery. Among the mothers, 18.1% (13 of 72) typed HPV-positive by the ViraPap/ViraType DNA hybridization technique. Two neonates (2.8% or 2 of 72) tested positive from oral-pharyngeal specimens. This finding supports the hypothesis that respiratory tract papillomatosis may develop as a result of perinatal vertical transmission of HPV. Furthermore, this study suggests that neither cesarean section nor prepartum treatment of HPV lesions will always protect against neonatal acquisition of HPV.

KEY WORDS — DNA hybridization, human papillomavirus, perinatal transmission, recurrent respiratory papillomatosis.

INTRODUCTION

One of the human papillomavirus (HPV)–related diseases that becomes symptomatic during infancy and childhood is recurrent respiratory papillomatosis (RRP). Human papillomaviruses 6 and 11 are the primary types that have been isolated from RRP, as well as from genital condylomata in adults.[1-4] There is an association between RRP developing in infants <2 years of age and a maternal history of genital condylomata and laryngeal papillomas.[1,2,5] A correlation between these maternal HPV-related diseases and concurrent HPV types in their children also has been found.[4-6] These studies were performed retrospectively in patients with juvenile-onset RRP; thus, it is unclear whether maternal HPV infection existed at term or delivery.

Recent studies suggest that HPV, like herpes simplex virus and cytomegalovirus, also can be transmitted to newborns at birth.[7,8] This was suggested in part because perinatal transmission of these other DNA viruses is well recognized.[9,10] Human papillomavirus is thought to be transmitted by neonatal aspiration of vaginal secretions rather than through maternal transplacental transmission. However, it is unknown whether HPV merely colonizes or whether it also infects infants as a result of this mechanism.[8] Cesarean delivery is thought to be protective against transmission of HPV if the amnion is not ruptured. Vaginal delivery appears to be the predominant mode of perinatal transmission, suggesting that a large percentage of newborns are potentially at risk of HPV infection.

In one study, HPV was identified in 3 of 70 foreskins among neonates by Southern blot DNA hybridization.[7] No maternal HPV test results were available and the authors stated elsewhere that it was unclear whether the positive results were due to contamination or were a valid finding.[10] In another study,[8] both mothers and newborns were screened for HPV, but only mothers were typed. None of the infants who were delivered by cesarean, but 36.5% (n = 15) of those who were delivered vaginally, were HPV DNA–positive by Southern blot. Four HPV-positive babies had mothers who were HPV-negative based on either a first- or third-trimester maternal cervical sample, although three of the mothers had either prior cytologic or postpartum DNA evidence of HPV. Because neonatal samples were taken immediately after birth, the infants were thought to have been inoculated but not infected at that point.

This prospective study evaluated the potential for perinatal vertical infection of HPV. Pregnant women were screened for infection during the third trimester and at labor prior to delivery (LD). These two time periods were used to evaluate changes in infection rates and to control for false-negative results associated with the time between the initial third-trimester test and potential subsequent activation of HPV prior to delivery, when the infant could become exposed. We collected HPV specimens from neonates at least 24 hours after birth to reduce the probability of false-positive test results associated with inoculation rather than infection.

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This investigation was funded in part by grant 1 K07 CA 1181-01A1 from the United States Public Health Service and the National Institutes of Health/National Cancer Institute and by a Veterans Administration Clinical Investigator Award.

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METHODS

Between April and August 1989, patients between the ages of 18 and 45 with uncomplicated pregnancies who presented to the obstetrics clinic at The University of Iowa Hospital for a third-trimester checkup were solicited at random into the study (n = 72). Three types of data were collected for each pregnant woman: 1) a patient questionnaire of sociodemographics and risk factors associated with genital condylomata, cervical cancer, or laryngeal papillomas, 2) a medical chart review to identify prior abnormal Pap smears (ie, condylomata, HPV-related cellular changes, dysplasia or squamous intraepithelial lesions, or cancer), clinical manifestations of HPV-related conditions, and reproductive and medical history, and 3) HPV DNA hybridization of exfoliated cervical specimens collected during the third trimester, and during labor prior to delivery, to compare for activated HPV infection. Less than 5% of solicited patients refused to participate.

Maternal Collection Procedures. Over 75% of the third-trimester specimens were taken between 36 and 38 weeks, with the others taken between 39 and 42 weeks. Specimens were collected with a large cotton swab applied to the cervix and vaginal fornix. Only three women (4.2%) did not have a third-trimester specimen taken because they were in labor the day of their scheduled clinic appointment. Among those who did not have an LD specimen (30.6%), several delivered before they reached the hospital, two delivered <24 hours after their third-trimester clinic appointment in which a specimen had been collected, several others were in late stages of labor at admission, and a few specimens failed to be retrieved in others.

The average age of the pregnant patients was 23.6, with the range between 17 and 41. Most patients were white (>97%), and a high proportion had at least a high school education (86%), with 43% having more than 12 years of education.

Newborn Collection Procedures. The average gestational age at birth (by prenatal ultrasound) was 40 weeks, with the range between 36 and 42 weeks. Most births were by normal spontaneous vaginal delivery (86.1%, n = 62). The cesarean rate (13.9%, n = 10) was comparable to that among the low-risk pregnancy clinic population at The University Hospital. A neonatal medical record review was made regarding clinical findings of congenital diseases or abnormal medical conditions to evaluate in conjunction with active HPV infection.

Human papillomavirus DNA specimens were available from all infants born to the pregnant study group (n = 72). Only one neonate (and mother) was eliminated from the study because of serious neonatal sequelae that precluded timely DNA specimen collection. The HPV specimens were collected on average 36 hours after birth and were collected as late as possible after birth prior to discharge. Newborns' HPV infection results were compared to those of their mothers on the basis of type of delivery (normal spontaneous vaginal delivery versus cesarean). We maintained a similar time span for specimen collection between these two types of delivery (since discharge after cesarean section typically is longer). Oral-pharyngeal and vulvar cells or foreskin tissue specimens were collected from newborns.

Specimens were collected from the oral-pharyngeal area by use of a sterile culturette to swab the oral cavity, soft palate, retromolar pad area, and oropharynx. The areas were swabbed and the cells placed into a sterile saline tube. Cells were collected from the vulvar area with a culturette and likewise placed in a sterile saline tube. The foreskin, removed at least 24 hours after birth, was placed in a sterile tube. Oral-pharyngeal specimens were collected from all newborns (girls = 42, boys = 30), vulvar specimens from all but one female, and foreskins from circumcised male infants (n = 10).

DNA Hybridization Technique. Testing was performed with the ViraPap/ViraType kit (Life Technologies, Gaithersburg, Md). These techniques are comparable in sensitivity and specificity of HPV DNA detection to the established Southern blot hybridization protocol[11,12] (also our preliminary data).

In the first test (ViraPap) of this proprietary nucleic acid hybridization procedure, all samples are hybridized to a mixed ^{32}P-labeled complementary RNA probe specific for HPV types 6, 11, 16, 18, 31, 33, and 35. In the second test (ViraType), positive or ambiguous ViraPap results are retested against three sets of probes that subclassify these HPV types: 6/11, 16/18, and 31/33/35. Ambiguous samples from the ViraPap screen were considered positive only when they fell clearly into an HPV group on the ViraType test. All patients were tested with these procedures, including infants of HPV-negative mothers to verify the presumption that they also would be negative.

RESULTS

Gynecologic History. Based on a review of the patient's medical record, pathology reports, and an interview regarding reproductive and sexual history by an obstetrics nurse, 15.3% (n = 11) of the pregnant women were identified as having a history of condylomata, and 16.7% (n = 12) a history of dysplasia. None of the patients had a history or current diagnosis of laryngeal papillomas.

Among the patients with a history or current (during pregnancy) diagnosis of condylomata, lesions either were treated in the first or second trimester with carbon dioxide laser therapy or they spontaneously regressed prior to their third-trimes-

TABLE 1. HPV TYPES IN MOTHERS AND NEWBORNS

	HPV Types			
	6/11	*16/18*	*31/33/35*	*6/11 + 16/18*
Mothers				
Third trimester	2	5	5*	1†
LD	1	1	1	0
Infants	0	1	1	0

LD — labor and delivery.
*No LD specimen in three.
†No LD specimen.

ter HPV DNA specimen collection. With the exception of one patient, all the women tested negative for HPV DNA. The one patient who had first-trimester and postpartum lesions of condyloma tested positive for HPV infection, as did her infant.

All except two patients with a history or current diagnosis of cervical dysplasia received treatment prior to the third-trimester HPV DNA specimen collection and tested negative for HPV infection. Of the two patients who were not treated for their dysplasia prior to the HPV specimen collection, one tested HPV-positive (HPV 16/18). Three patients had both a past diagnosis of condylomata and subsequent dysplasia, but no current diagnosis of either HPV-related condition. All were negative for HPV DNA. All neonates of these patients also tested negative for HPV DNA.

Human Papillomavirus DNA Analysis. Among those women with a third-trimester clinic specimen (n = 69), 13 were HPV-positive (Table 1). Among those with an LD specimen (n = 50), 3 were HPV-positive (all 3 had positive third-trimester samples as well). The overall frequency of HPV among the pregnant women was 18.1% (13/72). A comparison between the third-trimester and LD specimens among those who had both samples taken produced the following results: 6 patients were HPV-positive at the third trimester, but HPV-negative at LD, and 3 patients were positive at both time periods (1 each with 6/11, 16/18, and 31/33/35). No one was HPV-negative at the third trimester and HPV-positive only at LD. The other 4 HPV-positive women were sampled during the third trimester but not at LD (3 with HPV 31/33/35, 1 with HPV 6/11 and 16/18). There were 6 cases of HPV 16/18, 5 of HPV 31/33/35, and 3 of HPV 6/11 (Table 1). One of the women had a double infection of HPV 6/11 and HPV 16/18. The HPV types were the same for the two specimens collected from each of these patients.

Two (2.8%) of the infants were HPV-positive; both were female. HPV DNA was identified in 1 of 62 (1.6%) neonates who were delivered vaginally and 1 of 10 (10.0%) who were delivered by cesarean section (Table 2). Both positive specimens were from the oral-pharyngeal cavity; one typed positive for HPV 16/18 and the other for HPV 31/33/35 (Table 1). The genital specimens in these infants tested negative for HPV. The two HPV-positive infants were born between 39 and 40 weeks' gestation, but specimens were taken somewhat later than average (44 and 72 hours after delivery).

TABLE 2. HPV RESULTS BY DELIVERY TYPE

	Maternal HPV DNA			
Neonatal HPV DNA	*NSVD*		*Cesarean Section*	
	+	−	+	−
+	1	0	0	1
−	10	51	2	7

NSVD — normal spontaneous vaginal delivery.

One of their mothers had chorioamnionitis and was delivered by cesarean section. When screened by ViraPap, her LD specimen was borderline, but was negative when typed (ViraType). This patient had no history of an abnormal smear, and a cytology specimen taken during her current pregnancy also was negative. No HPV DNA specimen was taken during the third trimester, since the patient was in labor when she arrived for that clinic appointment. Her infant tested positive for HPV 31/33/35. The other mother with an HPV-positive baby (HPV 16/18) had a normal vaginal delivery. Both of her HPV DNA specimens were positive for HPV 16/18 as well, and she had a diagnosis of and treatment for vulvar condylomata 2 months prior to delivery as well as having had several previous diagnoses. Subsequently this patient had a recurrence of vulvar warts diagnosed at her first postpartum visit. The association between maternal HPV-related genital diseases and HPV infection detected by DNA hybridization is summarized in Table 3.

Birth Defects Associated With Infection. When we examined the neonatal medical history for congenital or neonatal abnormalities, there was no association between HPV infection and physiologic abnormalities, growth retardation, hyperbilirubinemia, stillbirths, infections, rashes, or any other conditions, including laryngeal papillomas.

DISCUSSION

The results of this prospective study suggest that the frequency of perinatal vertical transmission of HPV infection is low: 2.8% in our study population. A positive maternal HPV DNA test, even when based on cervical specimens collected immediately

TABLE 3. ASSOCIATION BETWEEN HPV-RELATED GENITAL DISEASE AND HPV INFECTION

HPV Status	*Condyloma*	*Dysplasia*	*Both*	*No HPV-Related Genital Disease*
HPV-negative	7	8	3	41*
HPV 6/11	0	0	0	3†
HPV 16/18	1§	1	0	4
HPV 31/33/35	0	0	0	5

*One woman had HPV 16/18–positive infant.
†One woman had dual infection (HPV 6/11 and HPV 16/18).
§Had HPV 31/33/35-positive infant.

prior to delivery, was rarely associated with an increased risk of active HPV infection in the newborn. Neonates do appear to be at greater risk of HPV infection in the oral-pharyngeal tract than in the genital area. Although the two positive neonatal specimens were not the HPV types associated with respiratory tract papillomatosis, this may reflect the low frequency of HPV 6/11 in our study population.

Our finding of neonatal oral-pharyngeal HPV infection supports the clinically accepted belief that RRP can develop as a result of perinatal vertical transmission of HPV. The long latency period associated with activation of HPV infection and subsequent disease development is well recognized[3,13] and further supports the hypothesis that perinatal HPV transmission subsequently can lead to respiratory tract papillomatosis.

Like Sedlacek et al,[8] we found HPV-positive neonates who had mothers without clinically apparent HPV-related lesions. In our study, one mother had no history of either an abnormal Pap smear or HPV-related lesions. The other mother had a history of and treatment for condyloma during her first trimester, yet she was positive for HPV infection at both term and LD, despite the absence of lesions. This result indicates that treating maternal HPV lesions prior to delivery does not prevent neonatal HPV exposure.

In contrast, 12 other HPV-positive mothers did not appear to transmit infection to their newborns, nor did most women with a history of gynecologic HPV-related lesions. Only one of the HPV-positive mothers had a history of HPV-related disease, and none had clinical signs of HPV lesions during pregnancy. The majority of neonates who were delivered of HPV-positive mothers in the study by Sedlacek et al[8] also were negative for HPV infection. Thus, there is no apparent consistent pattern between maternal history of HPV-related lesions or current HPV infection and neonatal HPV infection. If follow-up of these patients and other prospective studies demonstrate that these perinatal infections are a risk factor for subsequent HPV-induced morbidity, then, as this study suggests, all pregnant patients and their newborns need to be tested for HPV infection.

Human papillomavirus 6/11 was less likely to be identified in pregnant patients than HPV 16/18 or HPV 31/33/35. This finding is consistent with prevalence data of sexually transmitted HPV types in US populations.[14] The HPV-positive neonates in our study also were more likely to have these HPV types. Sedlacek et al,[8] in their study of perinatal vertical transmission, found no HPV 6/11 in pregnant patients and, although they were not typed, presumably no HPV 6/11 in their newborns. Both HPV 16/18 and HPV 31/33/35 have been associated with risk of oral as well as genital carcinomas. It has been presumed that transmission of HPV infection identified in oral cancers resulted from sexual contact. However, our study suggests that an alternative mechanism may exist: that a reservoir of oncogenic HPV types may be transmitted at birth.

While it is unclear why one of the HPV-positive neonates had an HPV-negative mother, this may be due to an inadequate cervical specimen taken, or HPV copy numbers below that detectable by the DNA hybridization technique used. Sedlacek et al[8] and Rando et al[15] also identified several newborns whose mothers tested negative for HPV infection. In addition, they found a decrease in the number of patients with detectable HPV infections between the third trimester and the first postpartum examination, from 46.0% to 17.5%.[15] Our study showed a similar decrease in HPV positivity between the third trimester and the LD specimen.

The negative maternal test in the positive infant was taken in a woman with chorioamnionitis who delivered by cesarean section. It has been speculated that perinatal HPV infection would not occur in utero if the amnion were intact. Sedlacek et al found no HPV in infants whose mothers delivered by cesarean section with an intact amnion. Since it is likely that this patient had amniotic leakage, and because she also had a borderline HPV test at screening, it is possible that neonatal transmission occurred by this route. This suggests that the practice of performing a cesarean section to protect children against vertical HPV transmission and subsequent respiratory tract papillomatosis may not be effective. This conclusion also is consistent with the findings of other studies that have identified RRP in children who were delivered by cesarean section.[1,16]

Presently, the minimal duration required for inoculation, infection, and activation of HPV is unclear. Therefore, whether the time period between delivery and neonatal specimen collection is adequate for HPV infection to occur is unknown. Sedlacek et al[8] detected HPV DNA in one third of the neonatal nasopharyngeal specimens immediately after birth. In contrast, when we waited 24 to 72 hours after birth before collecting neonatal specimens to reduce the probability of false-positive tests associated with viral colonization but not infection, the frequency was less than 3%.

Future studies of vertical transmission should prospectively follow infants, retest them to evaluate changes in their HPV status, and determine their probability of developing subsequent RRP.

ACKNOWLEDGMENTS — The authors thank Steven Gray, MD, Stanley Perlman, MD, PhD, Gail McGuinness, MD, and Linda Cripe, MD, for their assistance in this project.

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Ann Otol Rhinol Laryngol 100:1991

PHARYNGEAL ULCERATION IN AIDS PATIENTS SECONDARY TO CYTOMEGALOVIRUS INFECTION

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Cytomegalovirus (CMV) infections in patients with acquired immunodeficiency syndrome are common and may present as retinitis, encephalitis, esophagitis, gastritis, enterocolitis, adrenalitis, or pneumonitis. Three patients are presented with pharyngeal ulcerations secondary to CMV. Similar cases have not been previously described in the literature. Symptoms, physical findings, and the treatment of this clinical entity are discussed. Although pharyngeal CMV ulcers are not life-threatening, they may herald multisystemic CMV infection that may require prompt antiviral chemotherapy.

KEY WORDS — acquired immunodeficiency syndrome, cytomegalovirus, ganciclovir, pharyngeal ulceration.

INTRODUCTION

Ulcerative oropharyngeal or nasopharyngeal lesions in patients with acquired immunodeficiency syndrome (AIDS) are associated with significant morbidity and must be differentiated from a neoplasm. The differential diagnosis of large oropharyngeal or nasopharyngeal ulceration includes Kaposi's sarcoma and lymphoma. Bacterial, fungal, and viral infections have also been implicated. Self-limited cytomegalovirus (CMV) infections causing large oropharyngeal or nasopharyngeal ulcerations with subsequent resolution have not previously been described. We report on three patients with nasopharyngeal, oropharyngeal, and soft palate ulcers secondary to CMV. The diagnosis of CMV ulceration needs to be established to assure the patient that clinical recovery is expected.

CASE REPORTS

Case 1. A 36-year-old man with AIDS and disseminated Kaposi's sarcoma involving the right calf, right foot, right forearm, hard palate, and buccal mucosa presented with a 3-week history of sore throat, dysphagia, and odynophagia. He had been treated with acyclovir for 3 weeks for a presumed herpetic infection. A pharyngeal examination revealed a 3-cm ulcer with pseudomembrane formation extending from the level of the uvula to the nasopharynx (Fig 1). A culture of the biopsy specimen was positive for CMV. The patient was treated symptomatically with pain medication and a topical anesthetic, resulting in spontaneous resolution of symptoms. The ulcer resolved over the subsequent 2 weeks.

Case 2. A 42-year-old man with AIDS, CMV retinitis, CMV esophagitis, and *Pneumocystis carinii* pneumonia presented with a 1-cm right soft palate ulcer with surrounding erythema while being treated with 9-(1,3-dihydroxy-2-propoxymethyl) guanine (DHPG or ganciclovir) (Fig 2). A biopsy of the ulcer revealed CMV inclusions in cells (Fig 3). Blood and urine cultures for CMV were negative. The patient was treated symptomatically with analgesics and ganciclovir (maintenance dose of 5 mg/kg per day). Follow-up 8 weeks later demonstrated resolution of the ulcer. Four months later, while still taking ganciclovir, the patient presented with deteriorating mental status. The cerebrospinal fluid culture was positive for CMV. Because of the progressive CMV infection, the patient was declared a failure on ganciclovir and started on Foscarnet, an experimental anti-CMV drug. The patient died 1 month later after further deterioration of his neurologic status and general health. A postmortem examination demonstrated CMV encephalomyelitis, retinitis, acute epidural panniculitis, and vasculitis.

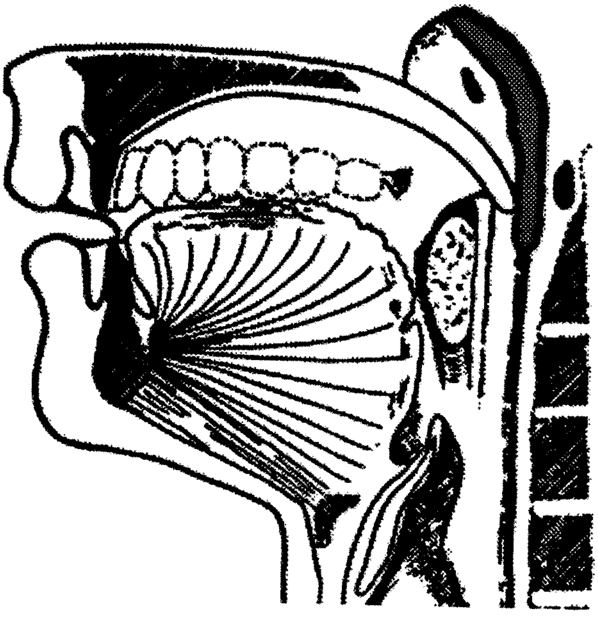

Fig 1. (Case 1) Nasopharyngeal ulceration (shaded area).

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Presented at the meeting of the American Academy of Otolaryngology–Head and Neck Surgery, New Orleans, Louisiana, September 24-28, 1989.

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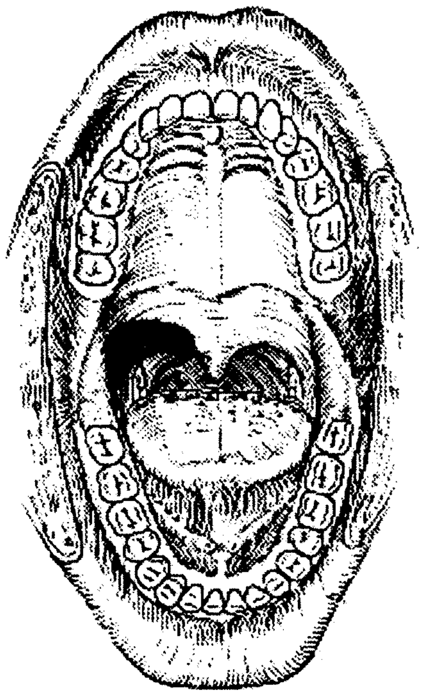


Fig 2. (Case 2) Shaded area highlights right soft palate cytomegalovirus ulcer.

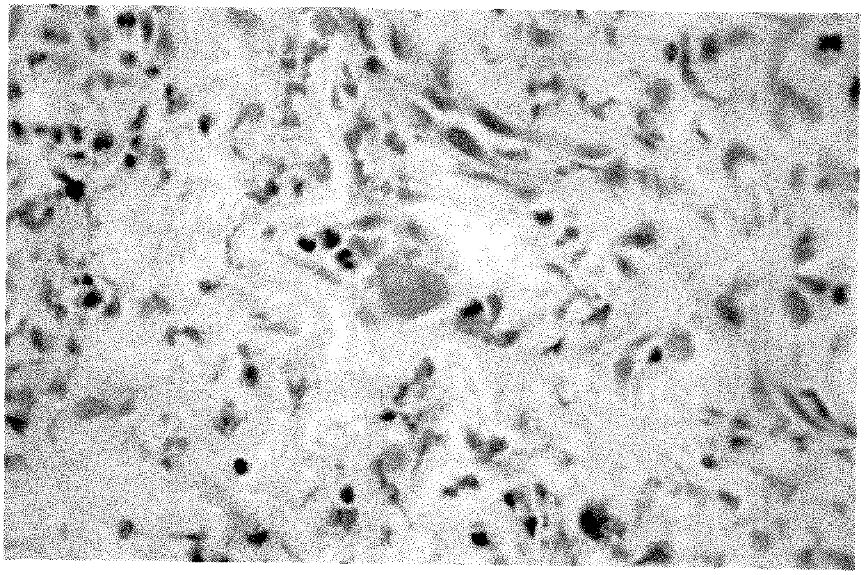
Case 3. A 45-year-old man with AIDS-related complex presented with a 6-week history of sore throat with otalgia, odynophagia, and dysphagia. An oropharyngeal examination revealed a 6-cm posterior pharyngeal wall ulcer extending from the uvula to the epiglottis tip (Fig 4). An esophagogastroduodenoscopy demonstrated esophageal and gastric ulceration. A culture of the gastric and pharyngeal biopsy grew CMV. Additionally, a urine culture was positive for CMV, while blood cultures were negative. The oropharyngeal ulceration resolved prior to treatment with ganciclovir for CMV gastritis.

DISCUSSION

Cytomegalovirus is a member of the herpes family of viruses, which includes herpes simplex 1 and 2, Epstein-Barr virus, and varicella zoster. Cytomegalovirus infections in patients with AIDS are common and may present as chorioretinitis, encephalitis, esophagitis, gastritis, enterocolitis, adrenalitis, or pneumonitis. Nearly 100% of patients with AIDS have serologic evidence of recently acquired or reactivated CMV infection. Seven percent to 10% of AIDS patients die of disseminated CMV infection and 50% to 90% have evidence of CMV at autopsy.[1,2] Cytomegalovirus has also been implicated as the cause of death in other immunocompromised patients, including transplant recipients[3]; it is a significant risk factor for leukopenia, graft failure, and death.[4]

Unlike esophageal and gastric ulcers, oropharyngeal or nasopharyngeal ulcerations secondary to CMV infection have not been previously described in the literature. Rabeneck et al[5] recently reported odynophagia and esophageal ulcers as the presenting symptoms in 16 homosexual men with acute (primary) human immunodeficiency virus infection. Three of the 16 patients had hard palate ulcers measuring 4 to 5 mm in diameter that resolved within 10 days. Acute and convalescent CMV and herpes simplex virus titers were normal and there was no histologic evidence of intranuclear inclusion bodies or giant cells; CMV and herpes simplex cultures from esophageal biopsy tissue were not performed. All three of our patients had a previously established diagnosis of AIDS or AIDS-related complex. Symptoms included throat pain, dysphagia, and odynophagia. Two of three patients had concomitant CMV esophagitis and gastritis; one patient had CMV retinitis. Physical examination revealed nasopharyngeal, oropharyngeal, and soft palate ulceration in the three respective patients. Pseudomembrane formation was noted over the nasopharyngeal ulcer, but was absent at the other two sites.

Fig 3. (Case 2) Biopsy of ulcer, demonstrating cytomegalovirus inclusion in cell (H & E).



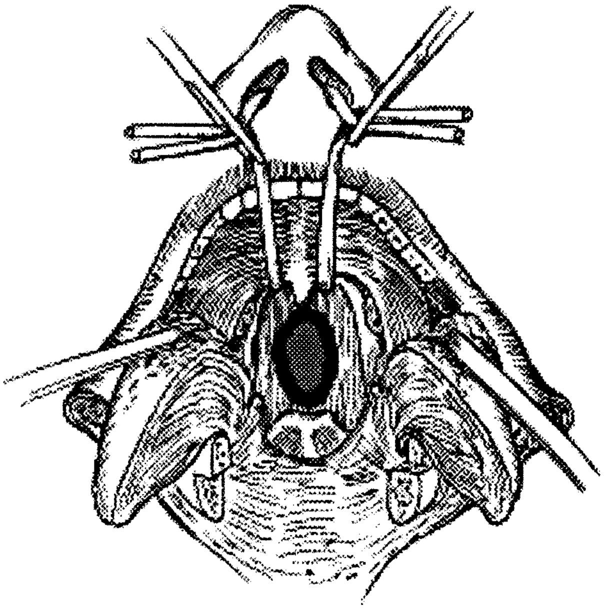


Fig 4. (Case 3) Large oropharyngeal ulceration extending from uvula to level of epiglottis.

Differential diagnoses of oropharyngeal or nasopharyngeal ulcerations in patients with AIDS include lymphoma, Kaposi's sarcoma, aphthous ulcer, fungal infection, CMV, or other viral infections, and are confirmed by tissue biopsies and cultures. Gram's stain, fungal and viral cultures, and histopathologic study of biopsy specimens are critical in identifying the etiologic infective agent. Gram's stain is helpful in detecting *Candida*. Viral and fungal cultures may isolate the herpes virus, CMV, and *Candida*. Since CMV can be frequently recovered from oropharyngeal or nasopharyngeal secretions without clinical evidence of disease, direct evidence of CMV involvement in tissues may be necessary for confirmation of CMV-induced disease. Histologically, cytoplasmic and intranuclear inclusions typical of CMV infection and nonspecific inflammatory cells are seen. The presence of cytoplasmic basophilic bodies of CMV helps to differentiate it from herpes simplex virus and adenovirus.[2]

The diagnosis of clinical disease due to CMV should be based on histopathologic evidence of infection; however, CMV inclusions may be absent and the definitive diagnosis is ultimately based on the identification of CMV on biopsy specimen culture. In the absence of positive culture and histopathologic results in clinically suspicious cases, the sensitivity and specificity of CMV diagnosis can be increased with techniques of nucleic acid in situ hybridization, polymerase chain reaction for CMV DNA detection, and immunohistochemistry using monoclonal antibodies against CMV immediate early antigens.[6] These techniques can be expeditiously applied to routinely obtained formaldehyde-fixed, paraffin-embedded tissue sections with detection of CMV within 24 hours.[7] In our series, CMV cultures were positive in all three patients.

Because of associated esophageal and gastric involvement in patients with oral CMV ulcers, radiographic or endoscopic evaluation of the upper gastrointestinal tract is recommended to identify focal or diffuse areas of erythema, mucosal edema, and mucosal ulcers. Clinically, gastric or esophageal involvement is suggested by typical gastric or duodenal ulcer pain, epigastric pain, and dysphagia.[8] Cytomegalovirus colitis should be suspected in patients with intermittent, crampy abdominal pain and diarrhea.[1] Stools may vary from 2 to 20 per day.

The treatment of isolated oropharyngeal or nasopharyngeal CMV ulcers is largely symptomatic, using analgesics and a topical anesthetic; however, concomitant CMV colitis, esophagitis, retinitis, encephalitis, or pneumonitis may necessitate systemic antiviral therapy. Treatment of CMV infections with interferon, acyclovir, vidarabine, and cytarabine has been largely unsuccessful.[3]

Ganciclovir, an acyclic analogue of thymidine and an inhibitor of viral DNA polymerase, has been shown to be clinically beneficial in the treatment of chorioretinitis[9] and gastrointestinal disease[10] caused by CMV. Ganciclovir is a virostatic agent related to acyclovir, but it has approximately 50-fold greater in vitro activity against CMV.[3] The response of CMV pneumonitis to ganciclovir, however, has been disappointing.[11] A long-term maintenance schedule is required to prevent the relapse that occurs when treatment with this virostatic agent is discontinued. Unfortunately, prolonged therapy may be associated with selecting drug-resistant CMV mutants, harboring grave prognosis for the patient and the future of antiviral therapy. Erice et al[12] reported the emergence of resistant strains of CMV in three patients who received prolonged courses of ganciclovir. In two of the patients, the ganciclovir-resistant strain emerged from previously sensitive strains. In the third patient, the drug resistance represented selection of a resistant strain in a patient who had been previously infected with multiple strains of the virus. Our case 2 probably represents selection of a drug-resistant CMV strain resulting in the progression of disease and the fatal outcome.

In our three cases cited, the role of ganciclovir in treating CMV oral ulcers is unclear, particularly since one patient developed the ulcer while on maintenance therapy of ganciclovir for CMV retinitis. In the other two patients, the oral ulcers resolved spontaneously without specific treatment. With the emergence of ganciclovir-resistant CMV in patients with AIDS, it is prudent to restrict ganciclovir to life- or sight-threatening CMV disease.[13] Although oral CMV infection is self-limited and not life-threatening, multisystemic CMV involvement requiring clinical intervention with antiviral chemotherapy should be considered.

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AUDITORY NERVE COMPOUND ACTION POTENTIALS AND BRAIN STEM AUDITORY EVOKED POTENTIALS IN PATIENTS WITH VARIOUS DEGREES OF HEARING LOSS

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Click-evoked compound action potentials recorded in normal-hearing patients through a monopolar electrode placed on the intracranial portion of the eighth nerve were compared with the responses recorded in patients with high-frequency hearing loss or with high- and low-frequency hearing losses. That multiple peaks appear in the compound action potential in patients with hearing loss implies that click sounds elicit successive and separated volleys of neural excitation in the ascending auditory pathway, whereas click sounds in patients with normal hearing mainly give rise to a single volley of neural activity. This difference in the pattern of auditory nerve activity might explain why there are often multiple peaks in the brain stem auditory evoked potentials in patients with hearing loss and that the peaks are often less well-defined than peaks in patients with normal hearing.

KEY WORDS — auditory nerve, evoked potentials, intraoperative recordings.

INTRODUCTION

It has been shown that the compound action potentials (CAPs) recorded from the exposed intracranial portion of the eighth nerve in response to transient sounds are triphasic in patients with normal hearing, with a small initial positive peak being followed by a large negative peak that is followed by a small positive peak.[1-6] This is characteristic for a monopolar recording from a long nerve in which a single propagated volley of neural activity travels.[7] The positive peak is generated when the neural volley travels toward the recording electrode, and the negative peak is generated when the volley maximum passes under the recording electrode; the small positive peak that follows the negative peak is generated as the neural activity moves away from the electrode site.[7]

The latency of peak II in the human brain stem auditory evoked potentials (BAEPs) is very close to that of the main negative peak of the CAPs that can be recorded from the intracranial portion of the eighth nerve.[1,2,4-6,8,9] This observation has led to the conclusion that in humans both of the two earliest vertex-positive peaks in the BAEPs are generated by the auditory nerve.[1-4] In contrast, the auditory nerve in animals seems to generate only a single peak in the BAEPs. This difference between humans and animals can be ascribed to the fact that the auditory nerve in humans is much longer than it is in the animals that are usually used in studies of auditory evoked potentials (2.5 cm versus about 0.5 cm).[10] Thus, both the distal and proximal portions of the human auditory nerve seem to generate individual peaks in the BAEPs.

Studies of the neural generators of the BAEPs in humans in whom recordings were made intracranially have been performed in patients with normal hearing and normal BAEPs. Since BAEPs are used extensively in studies of auditory system disease, it would be valuable to know about the relationship between near-field potentials and BAEPs in cases in which the BAEPs show abnormalities.

Thus, we undertook the present study in which we compared responses recorded intracranially from the eighth nerve (the CAPs) with the BAEPs in patients operated on to relieve cranial nerve disorders (trigeminal neuralgia, hemifacial spasm, glossopharyngeal neuralgia, disabling positional vertigo, or tinnitus), both those with normal hearing and those with one or another type of hearing loss.

MATERIALS AND METHODS

The results presented in this paper were obtained during routine intraoperative monitoring of evoked potentials in patients undergoing microvascular decompression operations for hemifacial spasm, glossopharyngeal neuralgia, trigeminal neuralgia, disabling positional vertigo, or tinnitus. The experimental procedure as well as the intraoperative monitoring was approved by the Institutional Review Board of the University of Pittsburgh School of Medicine and the patients gave their informed consent.

All patients had complete audiologic and otologic evaluations before the operation, including pure tone audiometry, speech audiometry using recorded lists, tympanometry, and recording of the acoustic middle ear reflexes, all performed in a sound-insulated booth by a certified audiologist using modern calibrated equipment (for details see Møller et al[8]). Both the operative procedure[11,12] and the tech-

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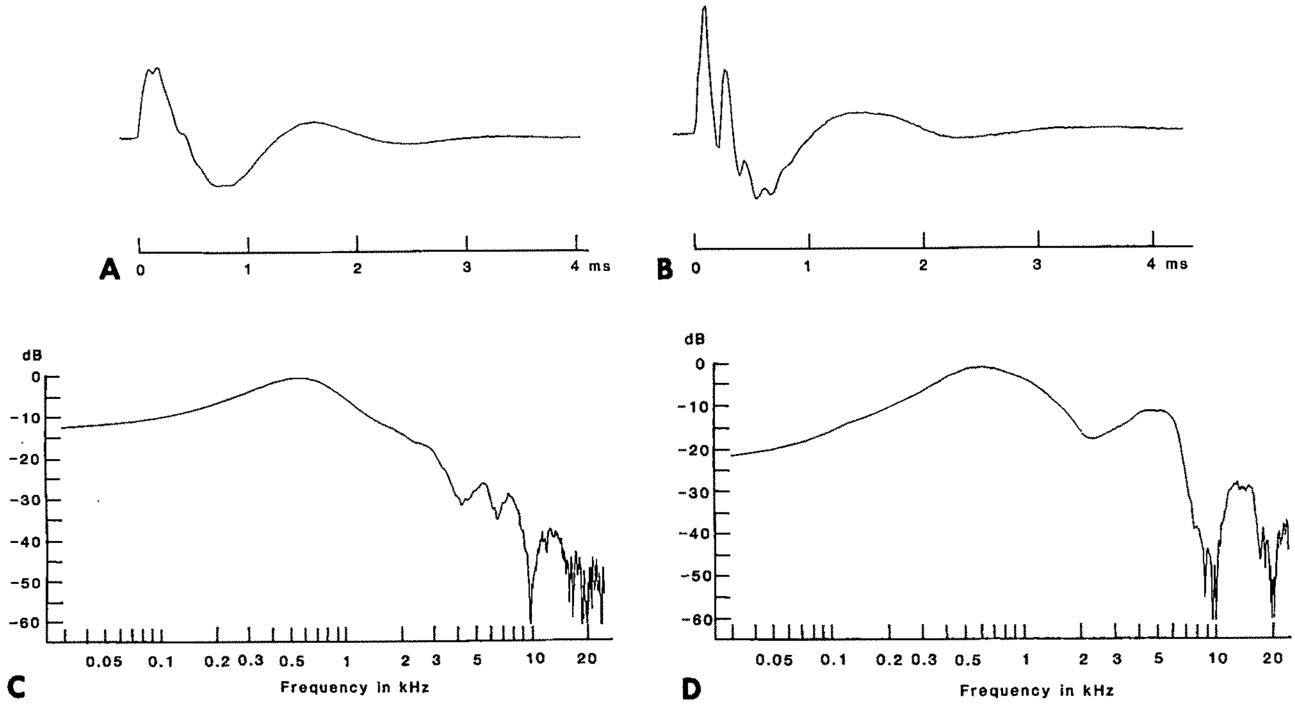

Fig 1. Test of earphone. A) Sound pressure produced by earphone used as measured in 2.5-cm^3 slightly acoustically damped cavity. B) Sound pressure measured at entrance of ear canal in human subject. C) Spectrum of sound pressure recorded in 2.5-cm^3 coupler. D) Spectrum of sound pressure recorded in human subject.

niques used to record BAEPs and CAPs from the exposed eighth nerve have been described in detail previously.[9,13-15] Therefore, only a brief description of the methods will be given here.

Click sounds were generated by presenting rectangular impulses of 100 microseconds' duration (Grass Instrument Co, type S10CTCMA) through miniature stereo earphones (Radio Shack, Realistic) that were secured in the ear of the patient with adhesive tape. The waveform of the condensation clicks was measured in a slightly damped 2.5-cm^3 cavity by a ¼-in condenser microphone (Bruel & Kjaer, type 3135). The sound pressure generated by the earphone when attached to the ear was measured by placing the same condenser microphone at the entrance of the ear canal in front of the earphone. The microphone rested in the recess between the tragus and the antitragus of the auriculum, and the earphone was placed in the ear in a way similar to what is done during intraoperative recording. As seen from Fig 1A, there is no discernible ringing in the generated click sound when measured in the damped cavity. When the sound pressure was measured with the same microphone placed at the entrance to the ear canal, a few peaks with intervals of about 0.2 millisecond could be discerned in the waveform of the clicks (Fig 1B). The peak equivalent sound pressure level used in this study was 105 dB. On Fig 1C,D, which shows the spectra of the responses shown in Fig 1A,B, a broad peak may be seen at about 600 Hz, and another peak at 6 kHz. The peak at 6 kHz is more pronounced when measured at the entrance to the ear canal than when measured in a coupler, and it is separated from the low-frequency peak by a broad dip of about 15 dB around 2 kHz. The sharp dip at 10 kHz is a result of the dip in the spectrum of the electrical impulse used to drive the earphone. There was no detectable difference between the waveforms of the condensation and rarefaction clicks (aside from their being inverted), and their spectra were virtually identical.

The BAEPs were recorded differentially between the vertex and the ipsilateral earlobe. The ground electrode was placed on the sternum, and the subdermal platinum needle electrodes (Grass Instrument Co, type E2) that were used to record BAEPs were inserted after the patients had been anesthetized; these electrodes were secured to the skin with adhesive plastic tape (3M Co, Blenderm).

The CAPs were recorded from the eighth nerve with a monopolar electrode made from malleable, multistrand, Teflon-insulated silver wire (Medwire Corp, type 7/40T) with a small cotton wick sutured to the uninsulated tip of each wire.[13,15] A platinum electrode inserted in the opposite earlobe served as the reference electrode for CAP recordings, and a separate recording channel was used for the CAPs.

The responses were amplified (50,000x for BAEP and 20,000x for CAP) with conventional amplifiers (Grass Instrument Co, type 12) with filter settings of 3 Hz high pass (−6 dB and 6 dB per octave rolloff) and 3,000 Hz low pass (−6 dB and 24 dB per

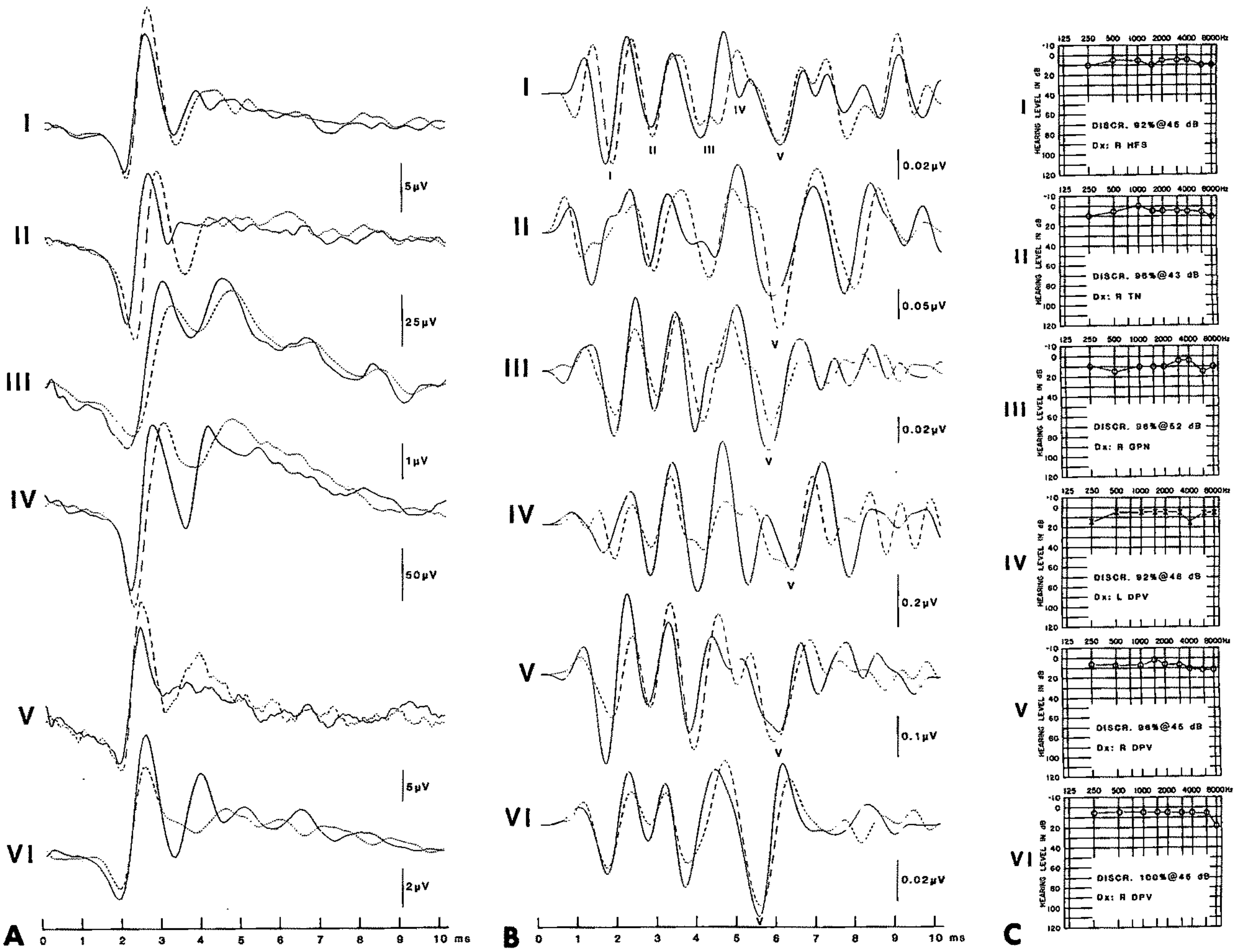

Fig 2. Six normal-hearing patients (I-VI). A) Compound action potentials (CAPs) recorded from exposed eighth nerve. B) Intraoperatively recorded brain stem auditory evoked potentials (BAEPs). C) Preoperative pure tone audiograms. Audiograms are for ear from which recordings were made intraoperatively, and BAEPs were obtained after patients were anesthetized but before operation was begun. Solid lines in BAEP and CAP recordings denote responses to rarefaction clicks, and dashed lines denote responses to condensation clicks. For CAPs, negativity is shown as upward deflection, and for BAEPs vertex negativity is shown as upward deflection. Same conventions were used in Figs 3-6. Patients underwent operations to relieve hemifacial spasm (patient I), trigeminal neuralgia (II), glossopharyngeal neuralgia (III), and disabling positional vertigo (IV-VI).

octave rolloff) for both BAEPs and CAPs. The recorded signals were sampled at intervals of 40 microseconds or 80 microseconds and digitalized (Datatranslation 12-bit analog-to-digital converter), and each channel consisting of 256 datapoints was averaged with an LSI 11/73 processor.

Baseline BAEPs were obtained after the patient had been anesthetized but before the operation was begun; at least two runs, each of 2,048 responses to each polarity of the click stimulation, were completed before the operation was begun. The BAEPs were recorded constantly throughout the operation until suturing of the skin. All data were stored on computer disks for later processing.

When the recorded data were plotted, zero-phase digital filtering was used to enhance the peaks in the BAEPs.[16] All BAEP records are shown with vertex negativity as an upward deflection; CAPs from the eighth nerve are shown with negativity as an upward deflection.

RESULTS

Normal Hearing. In patients with normal hearing (normal pure tone audiogram, normal discrimination score, and no subjective hearing problems) the CAPs recorded from the intracranial portion of the eighth nerve about halfway between the porus acusticus and the brain stem in response to click sounds have the triphasic shape typical of CAPs recorded from a long nerve with a monopolar electrode (Fig 2A). The latency of the large negative peak is slightly shorter in response to rarefaction clicks than in response to condensation clicks, but the difference is not noticeable in all patients. The waveform of the initial components of the CAPs is similar in all patients, but there is a second negative peak in the CAPs of some patients. The amplitude of this second negative peak varies from patient to patient and it can be as large as that of the initial negative peak. These second peaks are usually more pronounced in response to rarefaction clicks, and the latency is noticeably shorter in response to rare-

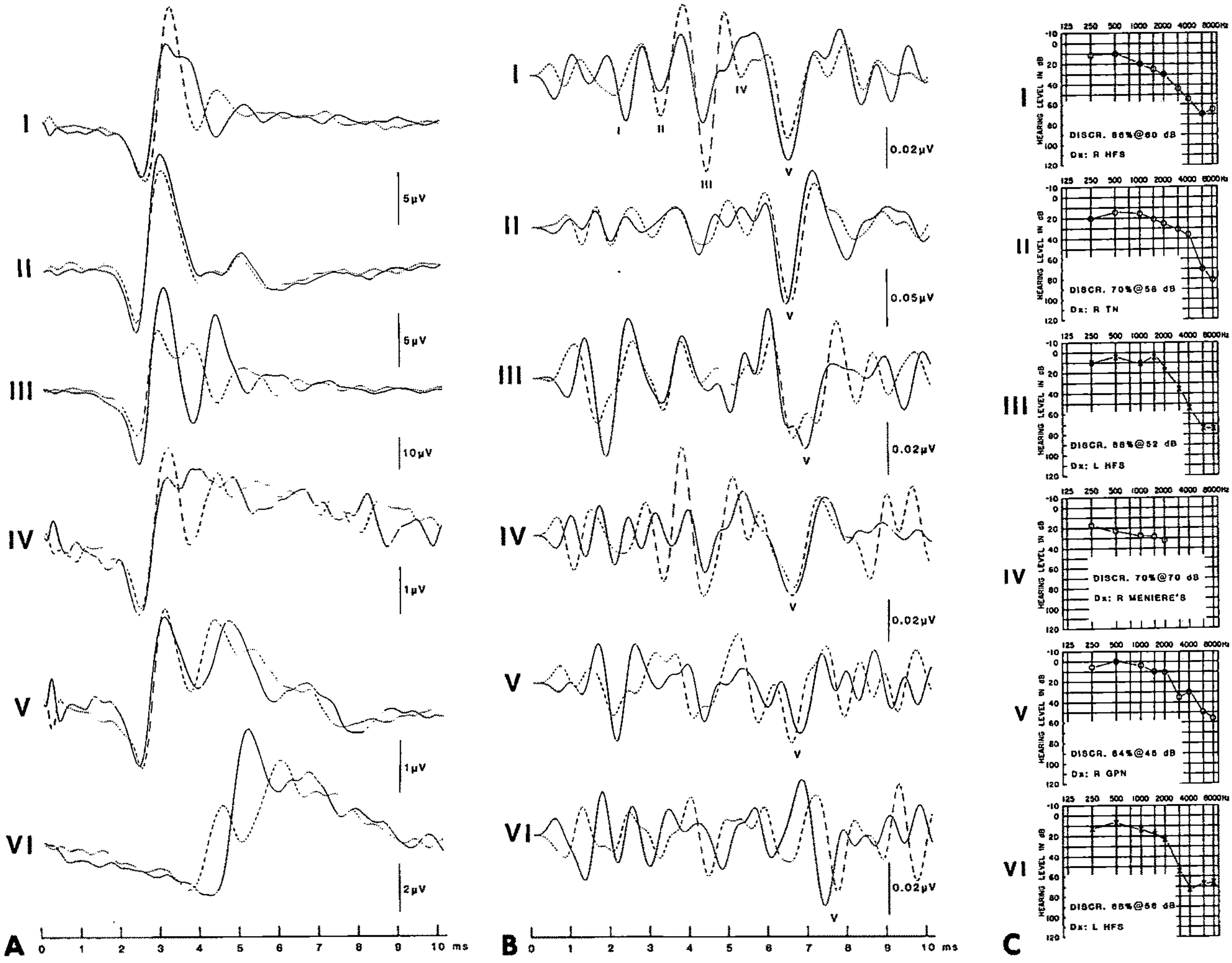

Fig 3. Recordings similar to those shown in Fig 2, but obtained in six patients (I-VI) with various degrees of high-frequency hearing loss. Patients underwent operation to relieve hemifacial spasm (I, III, and VI), trigeminal neuralgia (II), Meniere's disease (IV), and glossopharyngeal neuralgia (V).

faction clicks. The three bottom tracings in Fig 2 are from patients operated on to relieve vascular compression of the eighth nerve, but there is no consistent difference between the waveforms of the CAPs in these patients compared to those operated on to relieve vascular compression of the fifth, seventh, or ninth nerve (three top tracings in Fig 2).

The BAEP recordings in these patients consist of clearly defined waves, and there is little difference between the responses to condensation and rarefaction clicks (Fig 2B).

High-Frequency Hearing Losses. Generally, CAPs recorded from the exposed eighth nerve in patients with hearing loss have more complex shapes than do the CAPs recorded in patients with normal hearing (Figs 3 and 4).

High-frequency hearing loss results in a CAP with a prolonged latency of the initial negative peak; however, the latency of the earliest negative peak was only noticeably influenced by the polarity of the click stimuli in one patient in this study, the individual with a pure tone threshold that has a steep high-frequency slope above 2,000 Hz (bottom tracings in Fig 3A). The positive peak that precedes the negative peak in the responses from patients with high-frequency hearing loss is not distinctly different from the positive peak in the response of patients with normal pure tone thresholds. However, additional negative peaks with longer latencies are often seen in the CAPs of the patients with high-frequency hearing loss. Sound-evoked components can be identified clearly in the CAPs at latencies longer than 7 milliseconds in some patients, and these components are often greatly dependent on the polarity of the stimuli. The latencies and the amplitudes of these peaks are usually very different in response to condensation and rarefaction clicks (Fig 3A).

The peaks in the BAEPs in such patients (Fig 3B) are often less distinct than is the case in patients with normal pure tone thresholds, and there are often additional peaks, although the peaks are not grossly abnormal in these patients.

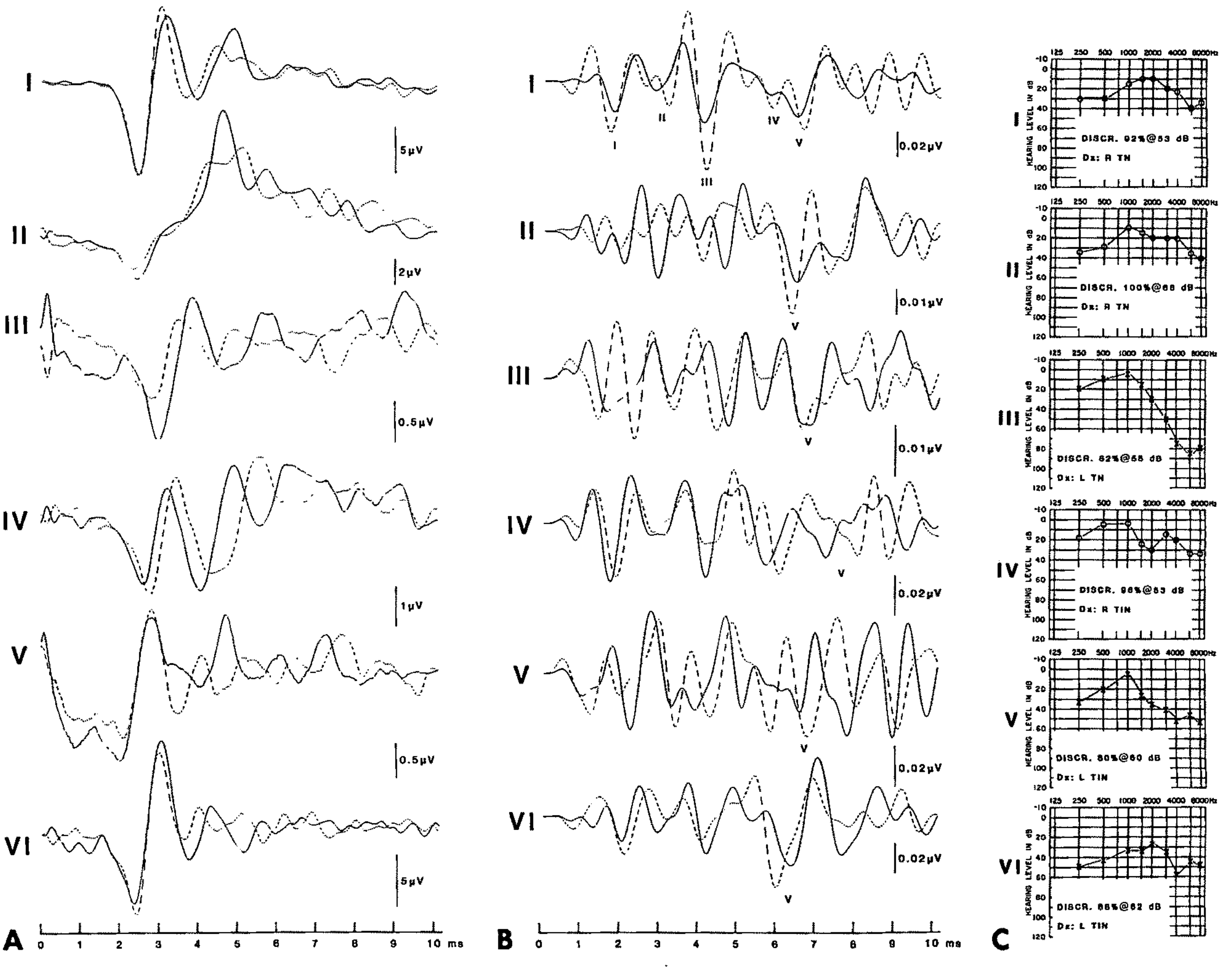

Fig 4. Recordings similar to those shown in Figs 2 and 3, but obtained in six patients with high- and low-frequency hearing losses. Top three patients (I-III) underwent operation to relieve trigeminal neuralgia, and bottom three (IV-VI) to relieve tinnitus.

High- and Low-Frequency Hearing Losses. Patients with both high- and low-frequency hearing losses have the most pronounced abnormalities in CAPs recorded from the exposed eighth nerve, but the initial negative peak of the CAP is normal in shape in most cases, although it has a prolonged latency and the amplitude is often lower than the amplitude in patients with normal hearing (Fig 4). The latency of the initial peak is nearly independent of the polarity of the stimulus.

The main abnormalities in the CAPs in patients with high- and low-frequency hearing losses are in components in the CAPs that follow the initial negative peak. The amplitude of the first of these waves is often as large as that of the initial negative peak; however, the waves that follow usually have smaller amplitudes. These late waves are different from the initial negative peak in that their latencies depend upon the polarity of the click stimuli, and their amplitude is usually larger in response to rarefaction clicks than condensation clicks. In many of these patients, there are reproducible stimulus-evoked components at latencies well in excess of 10 milliseconds.

The BAEPs of patients with both high- and low-frequency hearing losses are more complex than those of patients with normal hearing or of patients with only high-frequency hearing loss. The BAEPs in the patients who had both high- and low-frequency hearing losses showed extra peaks. In some of these patients there is a considerable dependence on the polarity of the click stimulus.

To find out if the late waves seen in the CAPs in patients with hearing loss represented propagated activity in the auditory nerve or possibly activity in stationary sources such as those that are located in the cochlear nucleus, we compared the potentials that could be recorded at two different locations along the intracranial course of the eighth nerve (Fig 5). It is seen that the latencies of these later peaks in the CAPs are prolonged by approximately the same degree as the initial negative peak when the location of the recording electrode was moved from a distal (near the porus acusticus) to a more central location, indicating that the late compo-

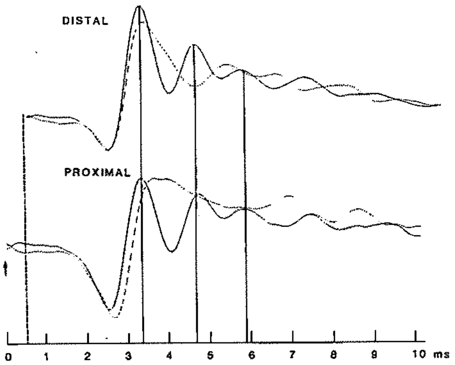

Fig 5. Comparison of compound action potentials recorded from eighth nerve near porus acusticus (top tracings) and from location about 8 mm more central (bottom tracings). Top tracings were shifted 0.5 millisecond to right, representing conduction time of nerve between two recording locations.

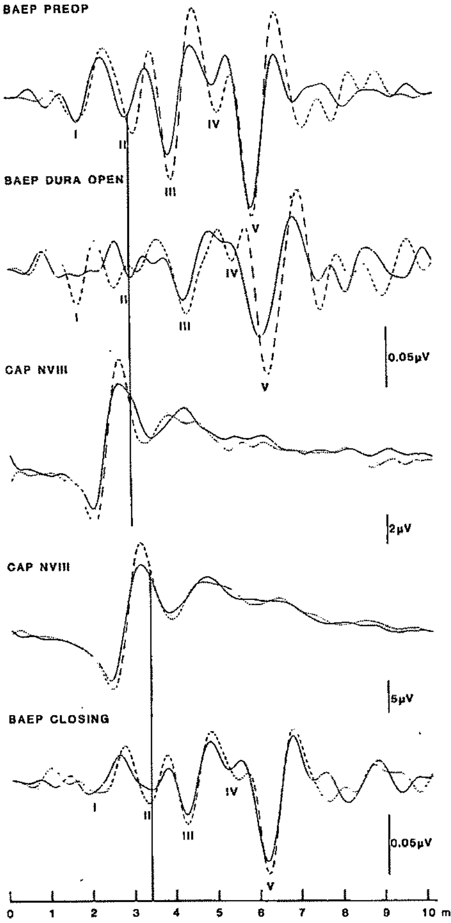

Fig 6. Examples of results obtained in one of patients in present study. BAEP — brain stem auditory evoked potentials, preop — preoperatively, CAP — compound action potentials, NVIII — cranial nerve VIII.

nents also represent propagated activity in the auditory nerve.

When abnormalities in the CAPs are studied it must be considered that the recorded potentials may be affected by surgical manipulations that occur before the eighth nerve is exposed, such as retraction of the cerebellum. We continuously compared the BAEPs recorded before the beginning of the operation with those obtained during the operation to detect changes that may have occurred as a result of the craniectomy, opening the dura, and releasing cerebrospinal fluid, as well as the necessary opening of the arachnoid membrane and the dissection needed to expose the eighth nerve. Small changes in the potentials, such as those seen in Fig 6, were regarded as normal, but if any larger changes occurred the patient was excluded from the study. The small changes that normally occur after opening the dura, as illustrated in Fig 6, can be attributed to differences in electrical conductivity of the tissues through which the electrical potentials are being conducted to the recording electrodes. For example, differences in cerebrospinal fluid level can change conduction of electrical potentials from the inside of the head to the surface of the skull, which itself has low conductivity.

DISCUSSION

The results of the present study confirm the results of earlier studies that showed that CAPs recorded from the exposed eighth nerve in patients with normal hearing are mainly triphasic and are dominated by a single negative peak.[1,2,4-6,13] The finding that the latency of the negative peak in the CAPs is slightly shorter in response to rarefaction clicks than in response to condensation clicks is in agreement with the general assumption that the excitatory stimulus is a deflection of the basilar membrane toward the scala vestibuli and thus the rarefaction phase of a sound.[17] However, more recent studies in which recordings were made from single auditory nerve fibers in animals have shown a more complex excitation pattern.[18-20] These studies show that both phases of a sound can be excitatory, depending somewhat upon the area of the basilar membrane stimulated. The relatively small increase in the dependence on click polarity of the latency of the main negative peak in the CAPs we saw in our patients with high-frequency hearing loss seems to support the results of animal studies showing that the latency of the auditory nerve CAPs is more dependent on the low-frequency spectral components of a click sound than on attenuation of high-frequency spectral components.[21]

The finding that the CAPs in patients with hearing loss often have multiple negative peaks of large amplitude is interesting in that it indicates that in such patients a click sound elicits multiple volleys of neural activity that are separated in time by amounts that depend on the polarity of the click sounds. Because the latencies of these different volleys of neural activity depend on the polarity of the clicks to a much greater extent than do the latencies of the earliest negative peaks, the volleys of neural activity most likely result from excitation at different locations (probably more apical) along the basilar membrane.

Considering that the click sounds used in the present study have a relatively flat spectrum up to about 7 kHz when measured at the entrance of the ear canal (Fig 1D), it may be assumed that the negative peak in the CAPs is mainly elicited by sound energy in the 5- to 7-kHz range in patients with normal hearing. It is therefore not surprising that the latency of this peak depends very little on the polarity of the clicks. Although it seems most likely that the late components that are seen in the CAPs in patients with hearing loss are elicited by low-frequency components of the click spectrum, it seems unlikely that these peaks result from the small nonuniformity in the click spectrum around 600 Hz. The late waves seen in the CAPs in patients with both high- and low-frequency hearing loss that have the form of low-frequency oscillations are similar to those reported earlier in certain patients.[22] The phases of these waves are exactly reversed in response to clicks of opposite polarity, and we have suggested that these waves replicate the oscillations of low-frequency portions of the basilar membrane. These waves are similar to the frequency-following response that has been reported from the auditory nerve in response to low-frequency tones.[23-25] These kinds of late components are not seen systematically, and although they may be related to specific disease entities, it is too early to make any definite conclusion about the relation of such abnormalities to known auditory symptoms.

Because the peaks in the CAPs that follow the initial negative peak often have amplitudes in the same range as the initial peak, it is likely that the latter peaks represent about as many nerve impulses as the initial peak. This conclusion is based on the fact that the CAPs recorded with a monopolar electrode from a long nerve can be assumed to be the convolution between the distribution of nerve impulses and a single nerve impulse.[26-28] It can therefore be assumed that these later peaks represent neural activity in the auditory nerve that causes multiple excitations of the auditory nervous system, following the initial excitation. Since at least the second neural volley in the auditory nerve is as large as the initial one in many patients with hearing loss, it may be assumed that the second excitation is as efficient as the first in activating higher auditory nuclei and fiber tracts. Depending on separation in time of these multiple excitations, extra peaks may appear in the BAEPs, or peaks may be distorted. In fact, the BAEPs in patients with hearing loss often have extra peaks not seen in the BAEPs of patients with normal hearing. As a result of the temporal integration of higher-order nuclei such as the superior olivary complex and the inferior colliculus, the activities at the level of the ascending auditory pathway that are evoked by two such volleys of auditory nerve activity may merge. This may explain why it is often the earlier peaks in the BAEPs that are abnormal in patients with hearing losses and peak V is often relatively normal in appearance. This would indicate that later peaks in the BAEPs such as peak V may be less sensitive indicators of disorders of the auditory periphery than are earlier peaks in the BAEPs.

The dependence on the polarity of the click stimuli of these late components in the response from the eighth nerve in patients with hearing loss indicates that in some patients, clicks of opposite polarities give a different input to the central auditory system. The use of alternating click stimuli should therefore be avoided in clinical BAEP testing. Clicks with alternating polarity are used frequently to help reduce the amplitude of the stimulus artifact. However, the use of modern earphones such as those used in the present study and avoiding strong electronic filtering by using digital techniques to remove stimulus artifacts before zero-phase digital filtering can reduce interference from stimulus artifacts to a negligible amount.[15,16]

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INTERNATIONAL SYMPOSIUM ON GRAVES' OPHTHALMOPATHY

An International Symposium on Graves' Ophthalmopathy will be held Aug 23-24, 1991, in Amsterdam, the Netherlands. The symposium will bring together members from different disciplines interested in the management of Graves' ophthalmopathy. The program will include lectures, free communications, and posters on topics on surgical, medical, and radiotherapeutic management, on immunological aspects, and on classification of the eye changes. The deadline for submission of abstracts is June 1, 1991. For further information, contact Amsterdam Thyroid Club, c/o W. M. Wiersinga, MD, Dept of Endocrinology, F5-258, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

Ann Otol Rhinol Laryngol 100:1991

CONTRIBUTION OF INCREASED ENDOLYMPHATIC PRESSURE TO HEARING LOSS IN EXPERIMENTAL HYDROPS

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After the induction of experimental hydrops there follows a strict sequence of compound action potential (CAP) audiogram changes. Within days a low-frequency loss (below 8 kHz) is detected; within weeks a very high-frequency loss (above 8 kHz) develops; and finally within months the 8-kHz region is also affected. Following the application of excess pressure, presumably to the endolymphatic spaces, via a cannula placed in the endolymphatic duct, a sequence of CAP audiogram changes occurs that is not similar to that observed with hydrops. There is first a very high-frequency loss (above 4 kHz), then a very low-frequency loss (below 4 kHz), and finally the 4 kHz region is also affected and thresholds for all frequencies become even more raised. The data thus suggest that a slow accumulation of endolymph as induced by blockage of the endolymphatic duct does not produce the same disorder as a rapid onset of a high pressure applied at the base of the cochlea. In addition the data suggest that raised endolymphatic pressure is not likely to be significant in early stages of hydrops, but could contribute to the later high-frequency sensitivity losses.

KEY WORDS — cochlea, endolymph, hydrops, Meniere's disease, model, perilymph, pressure.

INTRODUCTION

Meniere's disease remains a common idiopathic disorder of the inner ear. The fluctuant nature of the low-frequency hearing loss, together with the episodic nature of the vertigo and the tinnitus, renders the disorder elusive. No one treatment has been shown to be efficient in reducing the symptoms.

Ever since Hallpike and Cairns[1] demonstrated the presence of endolymphatic hydrops in temporal bones of Meniere's patients it has been assumed that hydrops is involved — but to what extent? Indeed, it is not known if the hydrops is the primary dysfunction or whether it is a mere epiphenomenon, given that hydrops can be found in association with other diseases. In either case an excess of endolymphatic pressure is considered likely, although some evidence suggests that the hearing loss may not be entirely due to that alone. First, Tran Ba Huy[2] has demonstrated that withdrawal of endolymph from the scala media in seven Meniere's patients did not improve but rather provoked a deterioration of hearing that recovered to the preoperative values in days. Second, we have recently shown that daily administration of the diuretic chlorthalidone to guinea pigs with experimental hydrops curbed the low-frequency loss but in the long term did not prevent the hearing loss. On the other hand, morphologic control at the end of 14 weeks showed that the hydrops had been reduced in those animals receiving the diuretic.[3] Finally, we have shown in the past[3-5] and again replicated in the present study that within a few days of hydrops induction a low-frequency fluctuant hearing loss can be detected. The sensitivity loss affects those frequencies below 8 kHz (above the first cochlear turn), while hydrops can be detected throughout the cochlea.

It was considered opportune to carry out experimental studies to compare the electrophysiologic consequences of these two experimental manipulations: hydrops and excess endolymphatic pressure. The technique for inducing hydrops[6] is now standard procedure and hydrops can be induced with a 100% success rate. On the other hand no technique is available for reliably recording intracochlear pressure. In order to circumvent this problem we have instead employed animals with normal cochleas and have augmented the endolymphatic pressure via a cannula placed within the endolymphatic duct. In this way the physiologic consequences of acute excess endolymphatic pressure could be assessed without opening the cochlear wall as in previous studies.

METHODS

Induction of Endolymphatic Hydrops. Pigmented guinea pigs (n = 6) were chronically implanted with a round-window platinum ball electrode by means of standard techniques. The animals were anesthetized (1 mL/kg) for the duration of the operation by a Ketalar-Rompun mixture in the ratio of 2:1 (ketamine hydrochloride 50 mg/mL, xylazine 2%). The animals were allowed to recover and 2 weeks later the compound action potential (CAP) audiogram was determined by means of tone pip stimuli (2-millisecond rise-fall, 30 stimulations per second) presented via a headphone (Sennheiser, HD424X) in a free field at 1 cm from the ear pinna. For the determination of the audiogram the animals were awake but sedated (Rompun 0.5 mL/kg) with the body and head movements restricted by the use of a body-holder with a nose ring. When the audiogram was shown to be normal the animals were then anesthetized (as above) and operated on to provoke

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endolymphatic hydrops. The posterior fossa was opened, the dura mater deflected laterally, the cerebellum displaced medially, the endolymphatic sac visualized, and the endolymphatic duct opened with a pointed instrument. Bone wax was forced into the opening in order to block the duct. A piece of Gelfoam was then placed on the exposed cerebellum and the skin sutured in place. The animals recovered within the hour and showed no behavioral signs of vertigo. The CAP audiograms were tested repeatedly during the 4 months that followed hydrops induction.

Increasing Endolymphatic Pressure. Under anesthesia the animals ($n = 15$) were implanted acutely with a platinum ball electrode on the round window. The CAP audiogram was immediately determined. When the audiogram was judged to be normal the endolymphatic sac was exposed in the same manner as described above. The distal end of the endolymphatic duct was pierced with a pointed instrument, and a needle (0.5 mm) was forced into the opening in order to cannulate the endolymphatic duct. The needle was connected to a length of tubing filled with endolymphlike solution (330 mOsm/kg H_2O, K^+ 153 mmol/L, pH 7.4),[7] which in turn was connected to a screw-type syringe. The syringe had a double exit with one opening toward the above-mentioned tubing and the second toward a mercury manometer. Under the conditions described here a pressure of at least 0.25 cm Hg was necessary before a flow of liquid occurred.

The CAP audiogram was determined repeatedly during the experimental procedure: after the dura mater was deflected, after the cannula was in place, and at intervals following the application of a fixed pressure.

Theoretically it might have been possible to check if the pressure applied at the endolymphatic duct was indeed transmitted to the scala media by raising the pressure at the duct and then by puncturing the scala media to see if the pressure at the duct would fall precipitously. However, technically this was not possible here, since a dorsal approach via the posterior fossa was made to the endolymphatic duct and a ventral approach via the mandible is required to expose the cochlear wall.

Histologic Control. After the animals were painlessly killed, the bullas were removed and perfused successively via the round and oval windows with 1% osmic acid in 0.1 mol/L sodium cacodylate buffer, followed by immersion and bathing in this fixative for 1 hour. The cochleas were then flushed with the buffer before being dehydrated to 70% ethanol. The cochleas were then dissected and the position of Reissner's membrane was noted to check for the presence of hydrops.

Some cochleas were further processed for observations by scanning electron microscopy. In this case the specimens were brought to 100% alcohol and critical point dried in carbon dioxide before being coated with gold/palladium.

Other cochleas were processed for resin-embedded transverse sections. In this case the cochleas were perfused with 2.5% glutaraldehyde in sodium cacodylate buffer (0.1 mol/L), decalcified in ethylenediaminetetraacetic acid, and embedded in Spurr's resin. Sections were made at 5 μm.

RESULTS

Endolymphatic Hydrops. The evolution of the CAP audiogram following the experimental induction of hydrops is illustrated in Fig 1. The six individual audiograms are distinguished by different symbols. The audiograms are presented together with the group mean audiogram from 25 normal-hearing animals (line without symbols) to show that at week 0 — that is, before hydrops induction — each individual audiogram was quite similar to the averaged normal one. One week following hydrops induction each animal had a substantial low-frequency sensitivity loss, while at 8 kHz and above, the thresholds remain normal. At 4 weeks post–hydrops induction two important aspects of hydrops are illustrated. For two animals the CAP thresholds for the low frequencies had improved relative to those recorded 1 week postoperatively. This is a clear demonstration of the fluctuating thresholds documented by us earlier.[4] The second aspect to be noted is the beginning of a very high-frequency loss, but in three cases the threshold at 8 kHz was still normal. By 8 weeks the high-frequency thresholds had further deteriorated, and all were above the mean normal audiogram. At 12 weeks after hydrops induction the sensitivity loss around 8 kHz was substantial, and by 16 weeks the CAP audiogram had progressed toward a flat conformation.

The presence of endolymphatic hydrops was always confirmed on dissection microscopy by Reissner's membrane's being displaced toward the scala vestibuli. In some cases the cochleas were resin-embedded and processed for transverse sections. An example is presented in Fig 2.

Endolymphatic Pressure. After the cannula was placed in the endolymphatic duct there was in some cases a sensitivity loss at the extreme high-frequency end of the audiogram, as shown in Figs 3-5. However, this loss was verified to be stable, since after the application of a pressure of less than 2.5 cm Hg (at which pressure a flow of solution could first be detected) the audiogram did not change during a period of 2 hours' observation.

When the pressure was augmented to 0.5 cm Hg the audiogram rapidly changed, and in all animals tested there appeared to be a strict sequence of changes. As illustrated in Fig 3 for one animal (GP621) the application of 0.5 cm Hg resulted in a

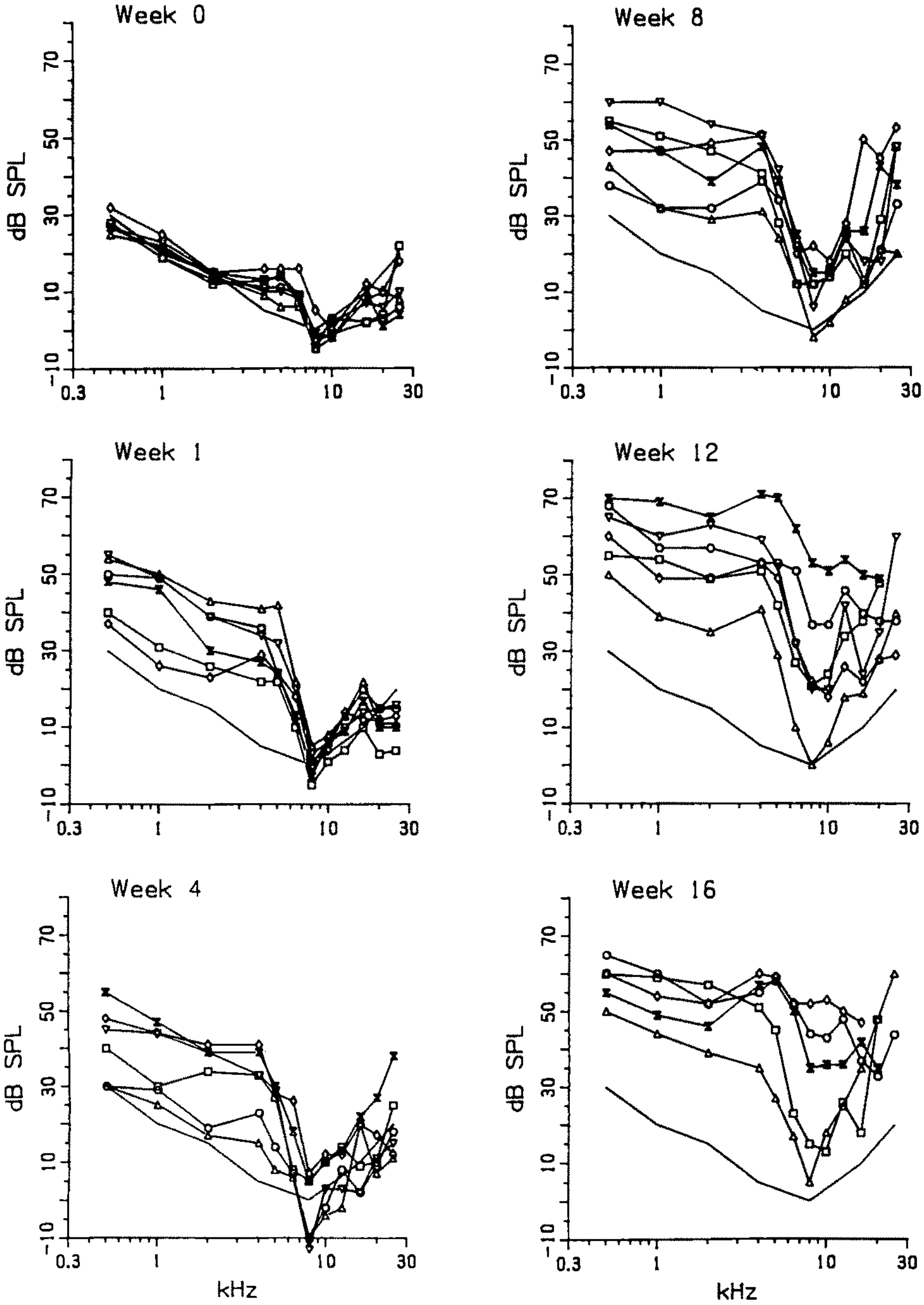

Fig 1. Evolution of compound action potential sensitivity loss following induction of endolymphatic hydrops. Week 0 represents prehydrops values. Solid line without symbols represents mean audiogram from group of normal guinea pigs (n = 25). Data from individual animals are represented by different symbols.

very high-frequency loss, while the thresholds at the low frequencies did not change as detected 20 minutes later. After 30 minutes of pressure all frequencies above 8 kHz were affected, while the threshold of 8 kHz as well as the low frequencies (with the exception of 500 Hz, which appeared elevated) remained stable. After 1 hour of pressure all high-frequency and low-frequency thresholds became elevated with the exception of 4 kHz, which appeared to be protected from the excess pressure. At 70 minutes after the application of pressure the threshold at 4 kHz was first detected to be altered. Within the next 20 minutes the thresholds for all frequencies were elevated, leaving the audiogram relatively flat and lying around 50 dB.

The application of a greater pressure (1 cm Hg) resulted in a faster evolution of events, as illustrated in Fig 4 for a different animal (GP622). After 30 minutes of pressure the thresholds at 4 kHz and 8 kHz were around 50 dB sound pressure level, while the thresholds for the frequencies above and below were substantially higher.

A very similar form of final audiogram was obtained during the first hour after the application of 0.5 cm Hg. One example (GP547) is illustrated in Fig 5. The same sequence of events as described above can be recognized. However, for this particular animal many CAP audiograms were monitored, and hence the sequence of sensitivity losses is more

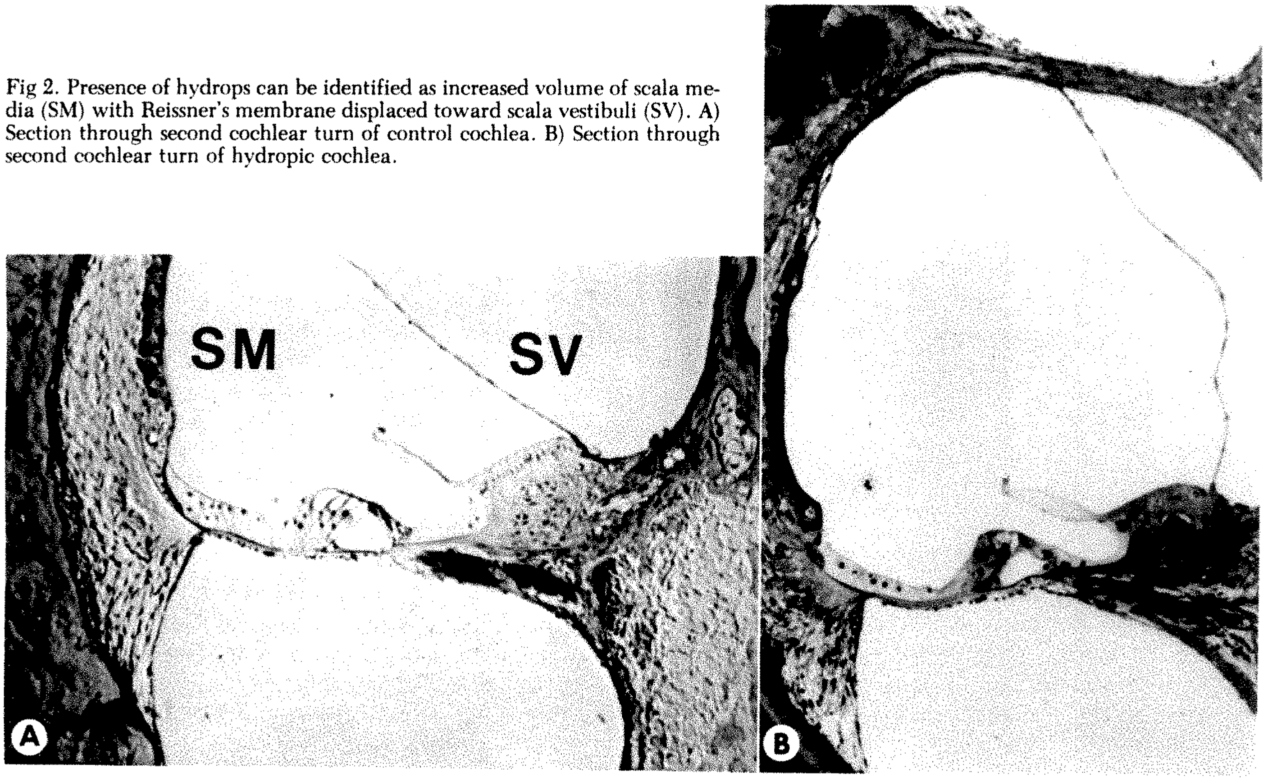

Fig 2. Presence of hydrops can be identified as increased volume of scala media (SM) with Reissner's membrane displaced toward scala vestibuli (SV). A) Section through second cochlear turn of control cochlea. B) Section through second cochlear turn of hydropic cochlea.

fully documented than for the other two presented above. There is an immediate very high-frequency (above 8 kHz) sensitivity loss, followed by a very low-frequency (below 4 kHz) sensitivity loss (Fig 5A). After 30 minutes of pressure the threshold at 4 kHz was first slightly modified, and within the next 30 minutes the whole audiogram became raised in a progressive sequence (Fig 5B).

The reversibility of the CAP sensitivity loss due to excess pressure was tested in eight animals. The cannula was removed and the animals were allowed to recuperate for 3 days. During this time the animals did not have any overt behavioral disturbances and vertigo was not observed. The CAP audiogram was again recorded and in three cases the audiogram was similar to that recorded at the end of the application of pressure. On the other hand, in five cases the audiogram had improved by at least 15 to 20 dB for those frequencies below 8 kHz. The example shown in Fig 5B is exceptional in that there was also some high-frequency recovery.

Following 3 days of survival the animals were killed painlessly and the cochleas were observed by light microscopy before being prepared for scanning electron microscopy. In these acute experiments in which pressure was applied for 30 or 60 minutes, Reissner's membrane was not found to be displaced as after the surgical induction of hydrops. However, hair cell damage was systematically observed by scanning electron microscopy. Typically the cochleas presented total outer hair cell loss at the base of the cochlea, while some damaged inner hair cells remained (Fig 6A). Around 5 mm from the base of the cochlea and corresponding tonotopically to about 7 kHz, some recuperation of the outer hair cells and inner hair cells was observed (Fig 6B). At 8 mm from the base of the cochlea all hair cells were present but some splaying of the stereocilia could be observed (Fig 6C).

DISCUSSION

Following the surgical blocking of the endolymphatic duct in the guinea pig, we have described here a sequence of CAP sensitivity losses together with fluctuations that reproduces exactly the typi-

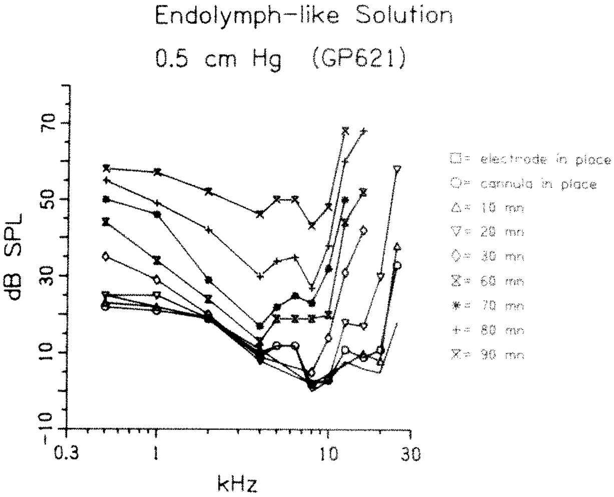

Fig 3. Evolution of compound action potential sensitivity loss following application of 0.5 cm Hg pressure to endolymphatic spaces via endolymphatic duct in individual animal (GP621). mn — minutes.

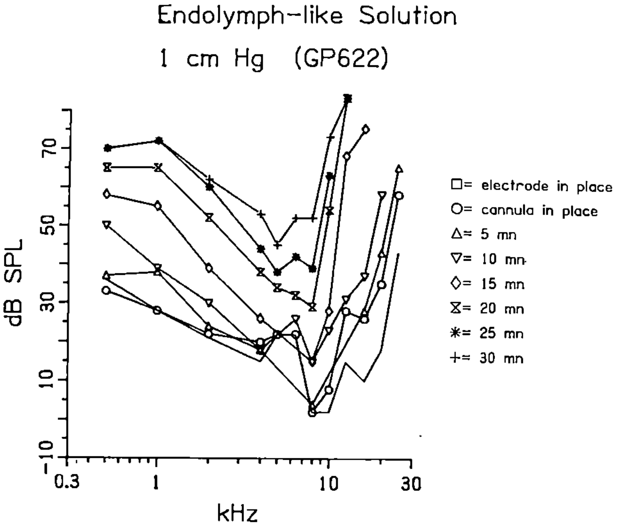

Fig 4. Evolution of compound action potential sensitivity loss following application of 1 cm Hg pressure to endolymphatic spaces via endolymphatic duct in individual animal (GP622). mn — minutes.

cal form of deafness associated with experimental hydrops as described by us earlier.[3-5] The data are very reassuring — that is, early stage hydrops can now unequivocally be associated with a low-frequency fluctuating loss and correlates closely with clinical observations in patients likely to have hydrops of the inner ears and in particular in Meniere's patients.[8] The CAP audiogram in experimental hydrops presents another characteristic and intriguing feature. The low-frequency loss is followed by a very high-frequency loss, but the 8-kHz region appears to be protected for some months. This is a particularly interesting feature, since in Meniere's patients the audiogram is often best preserved around 1 to 2 kHz.[9,10] In comparing data from humans to those from guinea pigs, a two-octave shift downward has to be considered and the time scale should be considered in years rather than months. When these scale factors are taken into account, experimentally induced hydrops is a very good animal model for the investigation of hydrops in humans.

One fundamental question that arises from these data is, What is the factor controlling this sequence of sensitivity losses associated with experimental hydrops? A generally held conception is that there is an increase in endolymphatic pressure in hydropic ears, and some authors believe that such excess pressure is likely to cause rupture of Reissner's membrane resulting in endolymph-perilymph mixing and hence accounting for the fluctuations.[11,12] In order to evaluate the contribution of possible excess endolymphatic pressure to the pathologic audiogram in hydrops, we have readdressed the question of cochlear pressure here.

Ideally we might have recorded intracochlear endolymphatic pressure in those hydropic cochleas described above; however, we are aware of the inherent problem of instantaneous pressure release once the cochlear wall is opened in order to introduce a measuring device. Other authors who have attempted to record endolymphatic pressure changes in experimental hydrops have found either no pressure difference between perilymph and endolymph in early hydrops[13] or only very small pressure differences of less than 1 cm water in long-standing hydrops in the guinea pig.[14,15] Given the problem of instantaneous pressure release, it is difficult to affirm the quantitative value of those data. We have preferred to avoid this problem by employing normally hearing guinea pigs and applying pressure to the endolymphatic spaces. Indeed, at least three other attempts in the past have been made to look at the effect of increased endolymphatic pressure.[16-18]

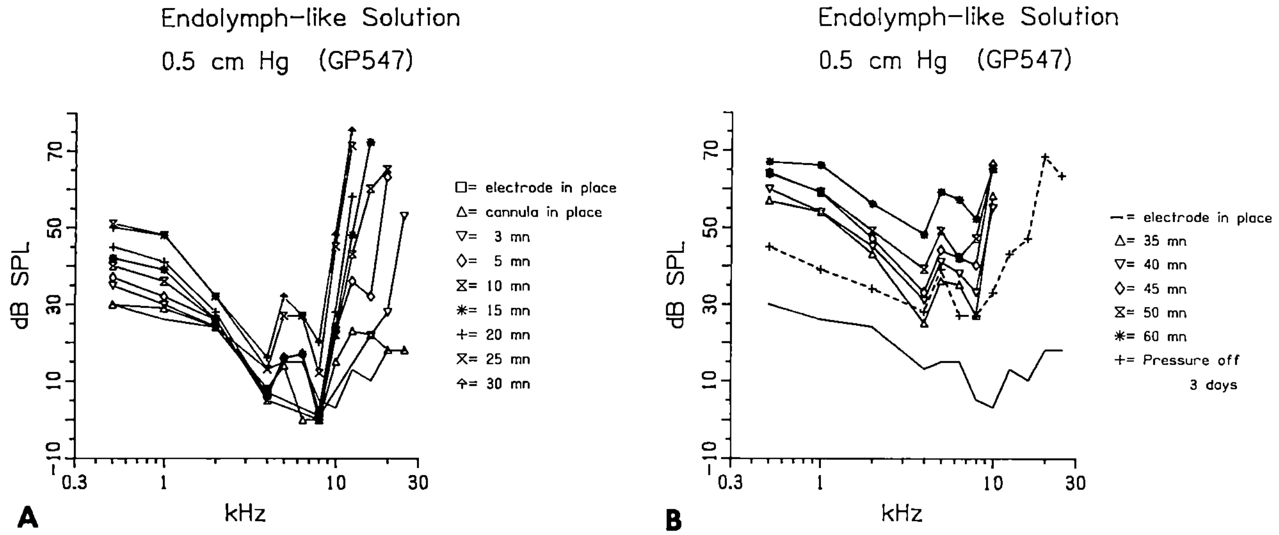

Fig 5. Evolution of compound action potential sensitivity loss following application of 0.5 cm Hg pressure to endolymphatic spaces via endolymphatic duct in individual animal (GP547). mn — minutes. A) Changes occurring during 30 minutes of pressure. B) Changes occurring during additional 30 minutes. Compound action potential audiogram improved after cannula was removed and animal was allowed to recuperate for 3 days.

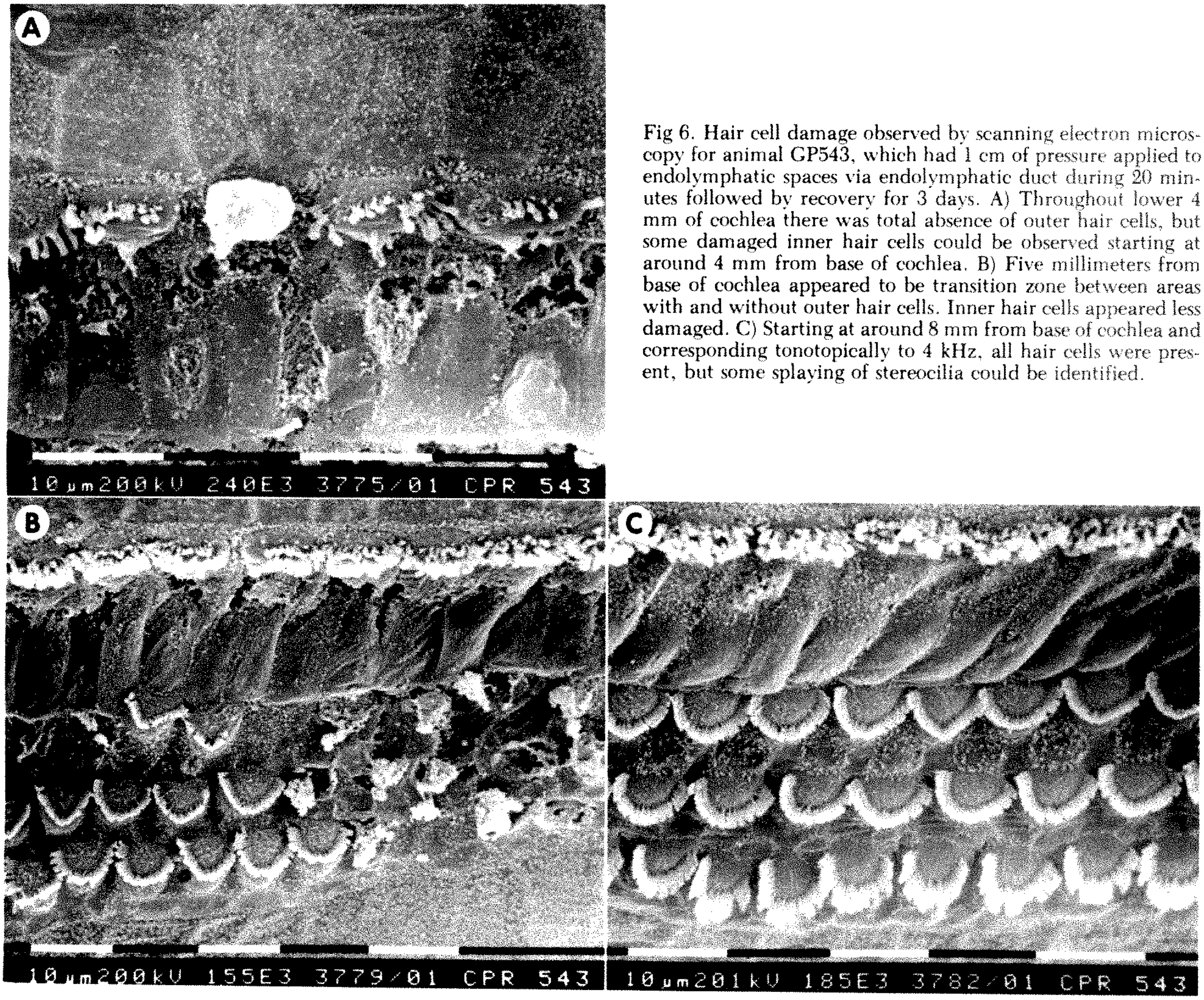
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Fig 6. Hair cell damage observed by scanning electron microscopy for animal GP543, which had 1 cm of pressure applied to endolymphatic spaces via endolymphatic duct during 20 minutes followed by recovery for 3 days. A) Throughout lower 4 mm of cochlea there was total absence of outer hair cells, but some damaged inner hair cells could be observed starting at around 4 mm from base of cochlea. B) Five millimeters from base of cochlea appeared to be transition zone between areas with and without outer hair cells. Inner hair cells appeared less damaged. C) Starting at around 8 mm from base of cochlea and corresponding tonotopically to 4 kHz, all hair cells were present, but some splaying of stereocilia could be identified.

Those three studies provided very limited data on the effect of pressure along the length of the cochlear duct, although all three were able to demonstrate that endolymphatic pressure diminished some auditory evoked cochlear-neural responses. Both McCabe and Wolsk[16] and Fukazawa et al[17] found diminution of the cochlear microphonics at 0.5 kHz as well as at 2 kHz and 1 kHz, respectively. Kitahara et al[18] looked at click-evoked responses and again found diminution of the responses.

The data from those three studies can be criticized on the basis that the penetration of the cochlear wall in order to introduce a micropipette might have caused cochlear damage that was not checked for by CAP recordings. The present study was aimed at minimizing such a technical problem by introducing a cannula into the endolymphatic duct and hence avoiding any direct contact with the cochlea. For reasons detailed in Methods, in the present study we assume but cannot prove that pressure applied to the endolymphatic duct was transmitted to the endolymphatic spaces. We believe this assumption to be justified for the following reasons. When the pressure was applied and no leaks were detected (manometer level stable), the electrophysiologic changes began within 5 minutes. On the other hand, when no pressure was applied or there was a leaky contact, no electrophysiologic changes ever occurred. Hence, our data suggest that increased endolymphatic pressure results in a rapid high-frequency loss, followed in time by a low-frequency loss and then a middle-frequency loss, and that finally all thresholds become progressively more raised. This sequence of events appears not to have a close correspondence with that observed in experimental hydrops. The substantial abrupt threshold shift between 8 kHz and 6.4 kHz observed in experimental hydrops could not be reproduced here with increased endolymphatic pressure. Furthermore, 8 kHz appears to be protected during the development of experimental hydrops, while when the endolymphatic pressure is raised, 4 kHz appears to be somewhat protected.

The data indicate that excess endolymphatic pressure cannot account for the early low-frequency sensitivity losses, which are fluctuant, but might contribute to the second phase of deafness, in which the very high frequencies become affected. These suggestions are in close concert with those we expressed after an earlier series of investigations. As demonstrated here, we observe substantial low-frequency hearing losses after 1 week of hydrops, and we have observed rapid fluctuations within days[4] and even during a recording session of several hours. These data rather suggest that the underlying mechanism controlling fluctuations must be such that it can be rapidly reversed. On the other hand, ruptures in membranes are likely to take some time for repair. In fact, we have recently presented a more realistic explanation for the fluctuations in the form of intermittent transduction. We have revealed a particular hair cell disorder in hydropic cochleas that had never been described before in hydropic ears or in any other type of cochlear disease. Scanning electron microscopy has revealed atrophy of the short and middle stereocilia (while the tallest stereocilia remain present and upright) on the outer hair cells above the first cochlear turn in experimental hydrops.[19,20] This discovery represents the first clear correspondence between the hydropic audiogram and the cochlear disorder. Hair cell loss has previously been described in temporal bones of experimental hydrops[6,21,22] and Meniere's patients,[9,11] but the loss is restricted to the apex of the cochlea and does not correlate with the hearing deficit.

In conclusion, the data from the present study have suggested that endolymphatic pressure is not the critical factor determining the hearing loss at the onset of experimental hydrops. Outer hair cell stereocilia atrophy is a likely candidate to explain the fluctuating hearing loss. However, the underlying mechanisms responsible for the selective low-frequency loss still remain to be revealed.

ACKNOWLEDGMENTS — The histology presented in this article was carried out by A. Guilhaume. The helpful technical assistance of C. Aurousseau is also acknowledged.

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ENDOSCOPIC HOLMIUM LASER LARYNGOTRACHEOPLASTY IN ANIMAL MODELS

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Subglottic stenosis remains a difficult clinical problem with varied management approaches. An accepted procedure has been anterior and posterior cricoid incisions through an external approach for treatment of severe stenoses without a tracheotomy. The holmium:yttrium-aluminum-garnet laser, 2.1 μm wavelength with a pulsed output, is transmissible through standard fibers and ablates soft tissue and cartilage with minimal surrounding damage. This study in in vitro and in vivo animal models shows that this new laser can be used to incise the anterior and posterior cricoid and tracheal cartilages with precise control and may be suitable for endoscopic laryngotracheoplasty.

KEY WORDS — anterior cricoid split, holmium laser, laryngotracheoplasty, subglottic stenosis.

INTRODUCTION

Subglottic stenosis is a well-recognized complication of endotracheal tube intubation, and its management remains a difficult clinical problem.[1] Therapeutic approaches have included medical therapy, dilation, local steroid injection, cryotherapy, endoscopic treatment with the carbon dioxide (CO_2) laser, open reconstruction, and the anterior cricoid split in selected patients. The anterior cricoid split procedure, through an external approach, is associated with an overall success rate that results in extubation of 70% of pediatric patients.[2,3] Investigators[4] have reported combined posterior and anterior cricoid incisions to improve the success rate further.

The present study was undertaken to determine the possibility of using an endoscopic approach with the holmium:yttrium-aluminum-garnet (YAG) laser (wavelength, 2.1 μm) to produce both anterior and posterior incisions in the cricoid cartilage. This endoscopic technique would diminish the morbidity associated with an open procedure and decrease operative time and length of hospitalization. The hol-

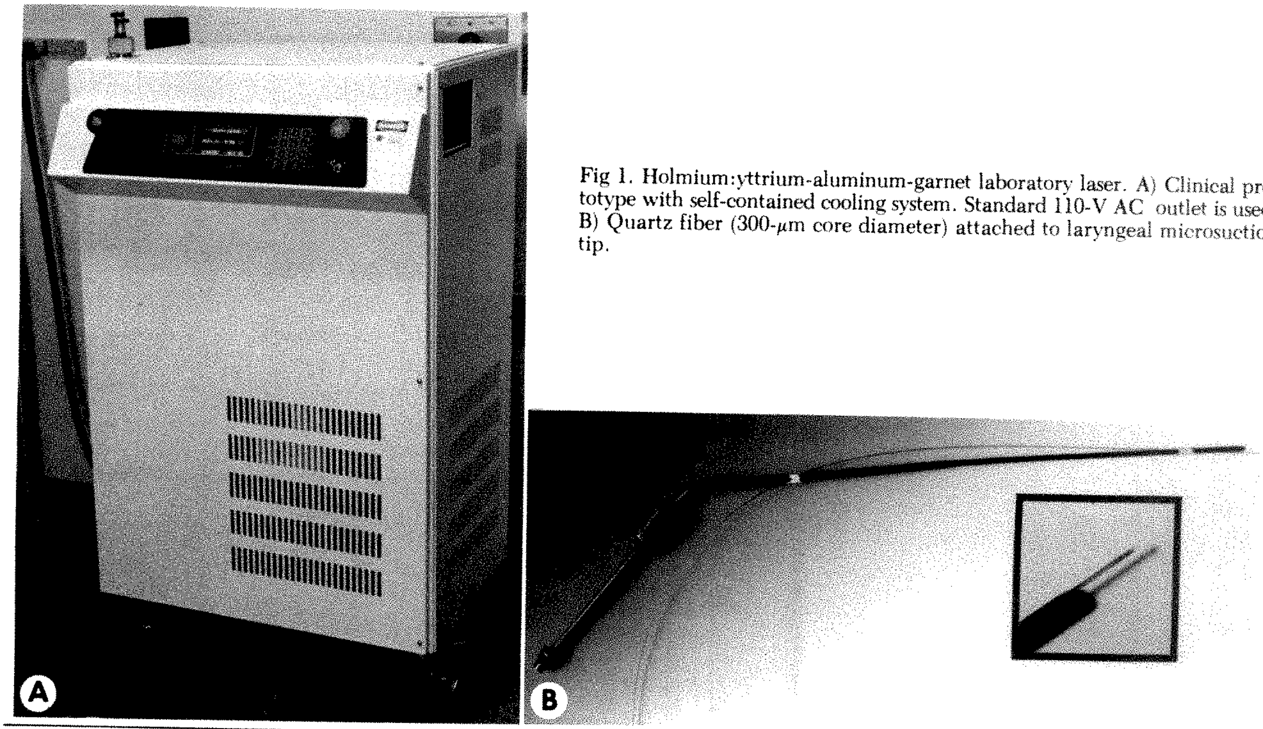

Fig 1. Holmium:yttrium-aluminum-garnet laboratory laser. A) Clinical prototype with self-contained cooling system. Standard 110-V AC outlet is used. B) Quartz fiber (300-μm core diameter) attached to laryngeal microsuction tip.

From the Department of Otolaryngology–Head and Neck Surgery (April, Shapshay), the Eleanor Naylor Dana Laser Research Laboratory (Shapshay, Rebeiz), and the Department of Anatomic Pathology (Aretz), Lahey Clinic Medical Center, Burlington; and the Department of Otolaryngology–Head and Neck Surgery, Boston University School of Medicine (April, Shapshay), Boston; Massachusetts. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Lahey Clinic Medical Center.

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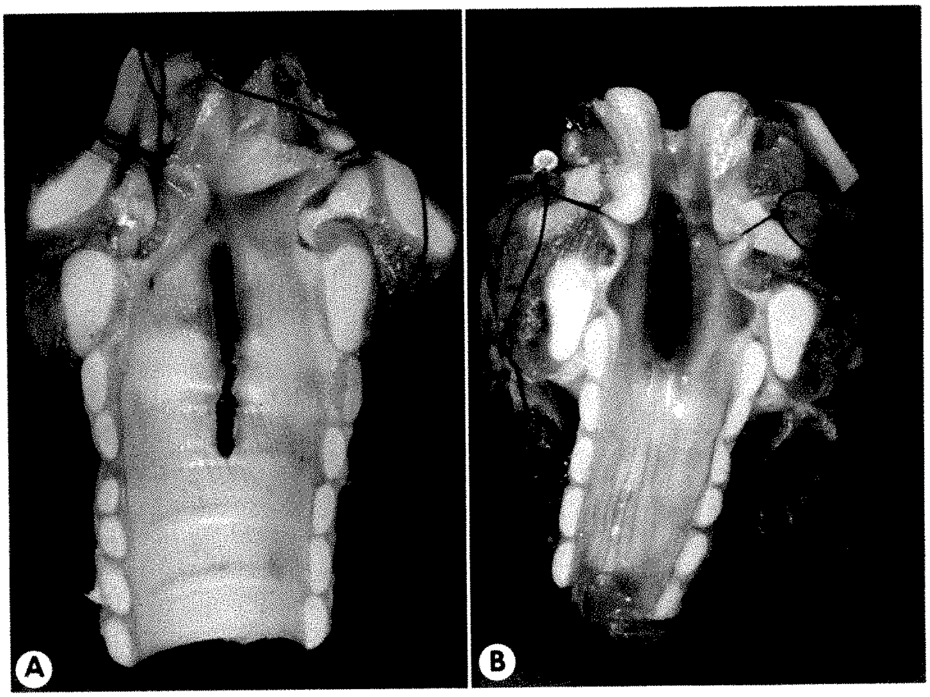

Fig 2. In vitro specimen after sagittal sectioning. A) Anterior incision through lower thyroid, cricoid, and upper tracheal cartilages. B) Incision through posterior cricoid lamina.

mium:YAG is a pulsed laser deliverable through readily available flexible quartz fibers. It has been shown to produce precise and predictable laser effects acutely, and chronically it has been associated with less granulation tissue and inflammation during the healing process compared with the CO_2 laser.[5]

MATERIALS AND METHODS

In Vitro Study. Nine fresh calf larynges with attached tracheas and surrounding tissues, including the hypopharynx, were mounted in a fashion to simulate endoscopic surgery. Subglottic exposure was obtained by use of a Dedo-Jako laryngoscope (Pilling, Fort Washington, Pa) and a Zeiss operating microscope (Carl Zeiss, Inc, Thornwood, NY) with a 400-mm lens. The holmium:YAG laboratory laser (a clinical prototype laser, Healthtek, Nevada City, Calif) is a YAG laser that has been chemically doped with thulium, holmium, and chromium (Fig 1A). It produces 200- to 250-microsecond pulses, which are transmitted through a flexible 300-μm-core diameter quartz fiber. This fiber was secured to a microlaryngeal suction with its tip protruding for adequate visualization (Fig 1B). Tissue vaporization was achieved with the fiber tip within 5 mm of the target tissue and with pulse energies between 800 mJ and 1,700 mJ per pulse and pulse rates between 2 and 6 per second (Fig 2). Histologic cross sections perpendicular to the cricoid incisions were studied after fixation in formalin, standard processing, and staining with hematoxylin and eosin. Mucosal, cartilaginous, and adjacent tissue ablation and associated thermal damage were measured by use of a stage micrometer in a coded fashion. Scanning electron microscopy was also performed following standard processing.

In Vivo Study. A 15-kg beagle dog was anesthetized with sodium thiopental (15 mg/kg). Endoscopy was first performed with the Dedo-Jako laryngoscope and Lewy suspension for adequate visualization of the anterior subglottic space. The fiber was attached to a microlaryngeal suction as a holder that provided adequate evacuation of smoke. The laser energy was delivered (1,000 mJ per pulse)

ENDOSCOPIC LARYNGOTRACHEOPLASTY WITH HOLMIUM LASER (SUMMARY OF IN VITRO AND IN VIVO RESULTS)

Specimen	Pulse Energy (mJ/pulse)	Cartilage Damage (μm)	Mucosal Damage (μm)	Deep Tissue Damage (μm)
In vitro				
1 A	800	138	552	1,821
P		276	1,001	1,069
2 A	850	140	2,300	491
P		170	2,300	550
3 A	900	184	2,023	867
P		138	828	460
4 A	1,000	140	1,300	1,880
P		140	1,880	320
5 A	1,150	184	1,300	Not through
P		120	2,020	370
6 A	1,400	184	1,001	None
P		184	1,001	None
7 A	1,450	140	2,000	575
P		200	1,300	2,000
8 A	1,500	180	1,300	1,010
P		180	1,880	275
9 A	1,700	260	1,590	Not through
P		231	1,734	1,156
Mean		177	1,517	802
Canine				
A	1,000	180	2,900	1,040
P		180	2,700	180

A — anterior, P — posterior.

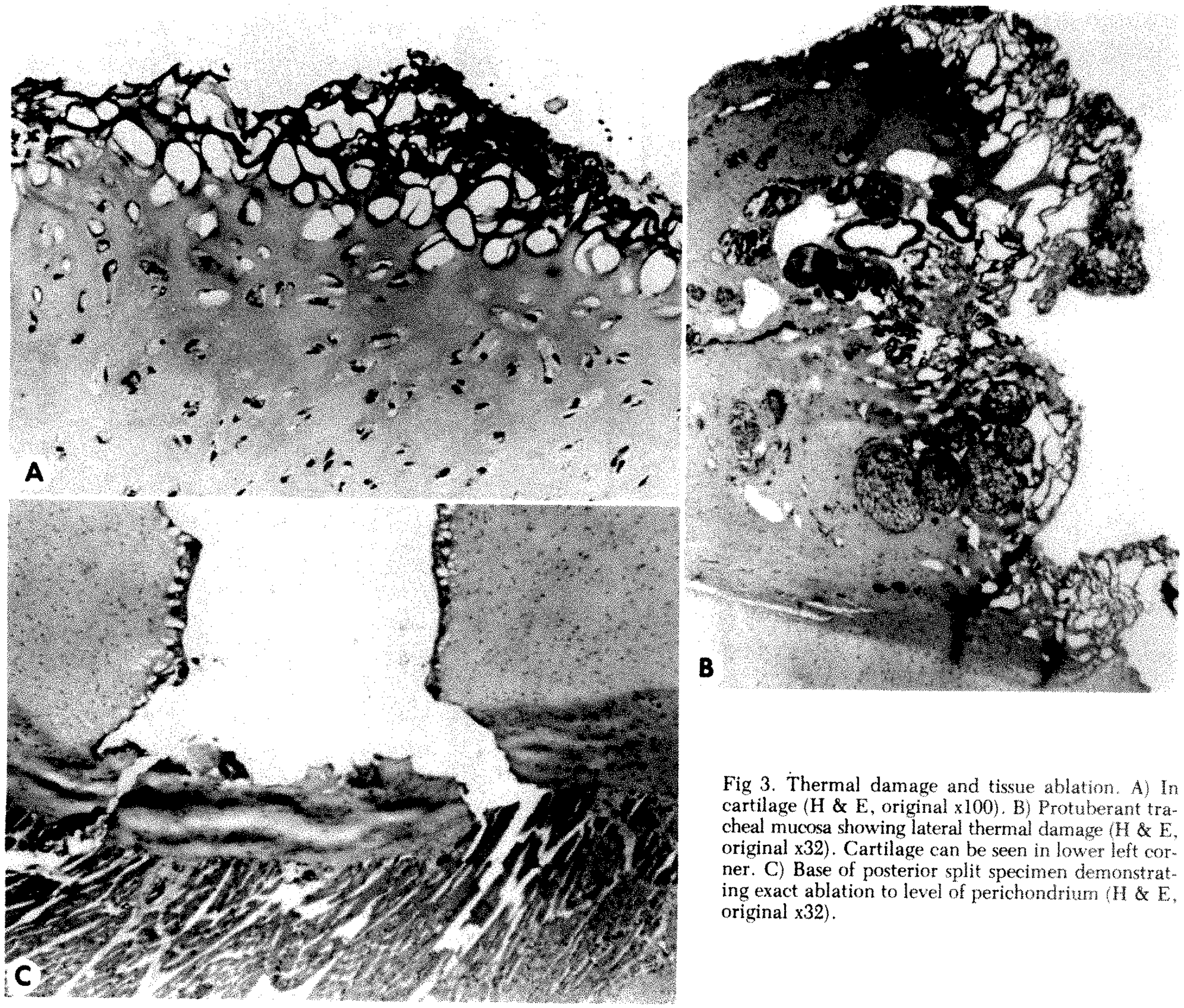

Fig 3. Thermal damage and tissue ablation. A) In cartilage (H & E, original x100). B) Protuberant tracheal mucosa showing lateral thermal damage (H & E, original x32). Cartilage can be seen in lower left corner. C) Base of posterior split specimen demonstrating exact ablation to level of perichondrium (H & E, original x32).

for the anterior incision through the lower thyroid, cricoid, and upper tracheal cartilages. The posterior incision was made after adequate exposure was obtained with the posterior commissure laryngoscope. The animal was painlessly killed, and the specimens were obtained and processed as described.

RESULTS

In the in vitro portion of the study, it took an average of 4 minutes to make the anterior incision and 9 minutes to make the posterior incision because the laryngoscope needed repositioning for adequate exposure. The tissue effects are summarized in the Table. Observation through the microscope (x6 magnification) showed the laser impact caused the edges of the mucosa to protrude. The amount of tissue ablated could be seen easily with each pulse of laser energy. The average damage to the surrounding cartilage was 177 μm (Fig 3A), and the average mucosal damage was 1,517 μm (Fig 3B). Ablation and thermal effect was seen in the deep tissue to an average of 802 μm (Fig 3C). In two specimens, the anterior incisions did not completely penetrate the cartilaginous ring. No damage to the hypopharyngeal tissue was seen in any of the specimens.

The in vivo procedure required 7 minutes for the anterior incision and 15 minutes for the posterior incision. The same precise control of laser penetration was seen, as was the protruding appearance of the mucosa with the initial impact. No bleeding was observed anteriorly; posteriorly, only a small amount of bleeding occurred that was easily removed with suctioning. Evacuation of smoke was not difficult.

DISCUSSION

In 1980, Cotton and Seid[6] described the anterior cricoid split procedure for subglottic stenosis to permit extubation without tracheotomy. Since then, authors[2,3,7] have confirmed the initial report with an overall success rate of approximately 70%. For unsuccessful cases, repeat anterior cricoid split and a posterior cricoid incision have been advocated before open reconstruction.[4] A midline posterior cri-

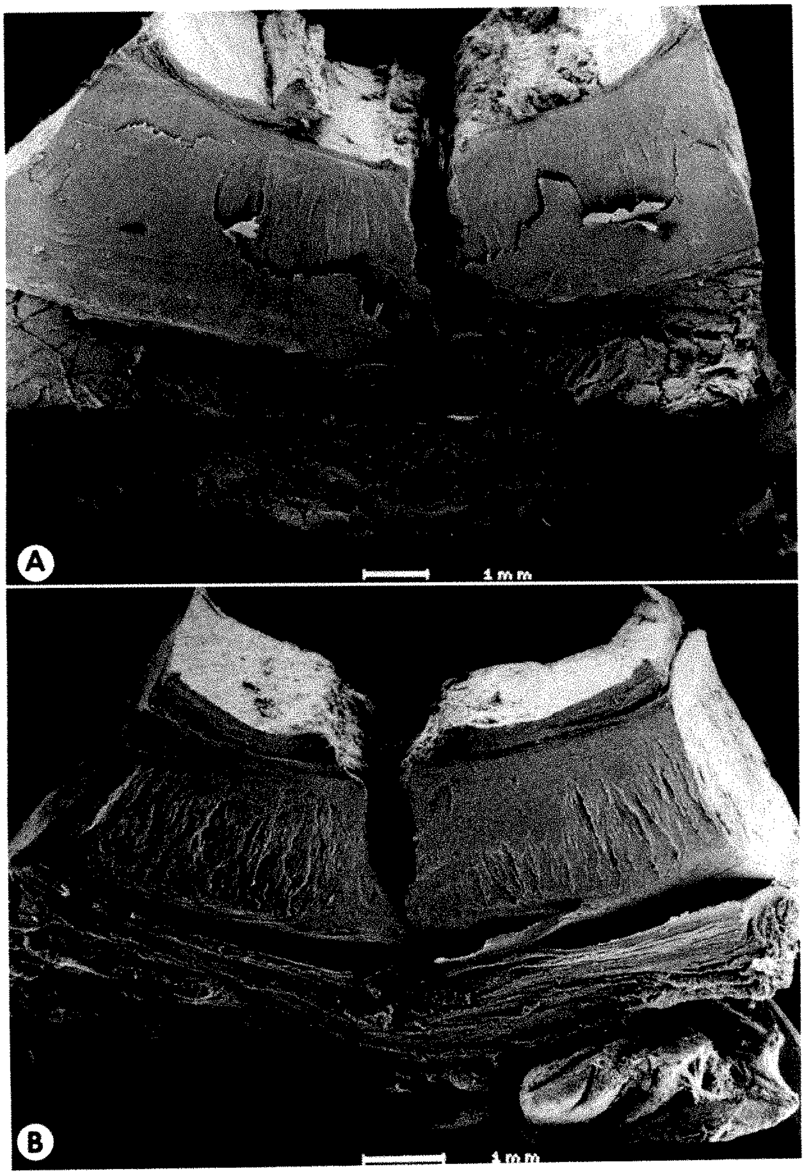

Fig 4. Scanning electron micrographs. A) Anterior specimens and B) posterior specimens showing well-defined and well-contained split of cartilaginous rings and protuberant mucosa surrounding mucosal incisions.

coid cartilage incision for subglottic stenosis was described by Réthi[8] and is currently an option for reconstructive surgery.[9] Division of the posterior lamina permits maximal increase in the subglottic area,[10] and the raw surfaces left in the larynx epithelialize surprisingly well.[11] Type and duration of stenting remain a controversial issue[12] and are not the subject of this paper.

Endoscopic management of subglottic stenosis with the CO2 laser has been performed since the 1970s with a success rate of approximately 50%.[13] Factors associated with a poor result or failure with the CO2 laser include circumferential scarring with cicatricial contracture, scarring wider than 1 cm in vertical dimension, tracheomalacia and loss of cartilage, and previous history of severe bacterial infections associated with tracheotomy.[14] The morbidity is usually minimal, and in the event of failure little is lost because an open operation can still be performed.[15] The noncontact neodymium:YAG laser has been used for tracheal stenosis, but results have been disappointing because of its primary coagulating effect on soft tissue.[16]

This project was undertaken to determine the possibility of using the holmium:YAG laser to produce anterior and posterior cricoid incisions while endoscopically examining the mucosal, cartilage, and surrounding tissue damage. The holmium:YAG laser emits light in the near-infrared spectrum at a wavelength of 2.1 μm with water absorption approximately one sixteenth of the absorption of the CO2 laser.[17] Unlike the continuous-wave CO2 laser, the holmium:YAG laser ablates cartilage and bone efficiently.[17] The pulse duration of this laser is less than the thermal relaxation time of tissue; therefore, most of the energy delivered will be expended heating and then vaporizing the tissue at the site of application with minimal collateral thermal damage.[18] The ability of the holmium:YAG laser to be transmitted through a noncontact fiber permits constant direct visual monitoring that, coupled with the use of the operating microscope for magnification, gives the endoscopic surgeon precise control over tissue removal.

Results of the in vitro and in vivo studies showed that tissue removal can be seen layer by layer with minimal charring. The initial laser impact produces a protuberant appearance of the mucosa with good hemostasis. In a previous study[5] in the canine trachea, initial surrounding edema subsided during 30 minutes of observation, and although healing was somewhat slower than with the CO_2 laser, there was less inflammatory response and granulation during the healing process. Microscopically, the amount of cartilage damage was small (177 μm, also in vivo), with an average of 1,517 μm (2,800 μm in vivo) of mucosal damage, neither varying appreciably with the pulse energies used. Control of penetration depth of surrounding tissue after completion of the cartilage incisions was excellent (Fig 4). Anterior to the cricoid cartilage, the tissue consisted of fascia, muscle, and the thyroid isthmus, which was not damaged. Posteriorly, no damage was seen to the tissue of the hypopharynx.

Future investigation will examine the acute and chronic effects of mucosal, cartilaginous, and soft tissue incisions in a ferret subglottic stenosis model.[19] The possibility of delivering the laser energy through a tracheoscope with optical control using tracheal telescopes also exists.

This study suggests that the holmium:YAG laser delivered by a noncontact fiber in a pulsed mode can produce precise anterior and posterior cricoid cartilage and tracheal incisions with minimal surrounding cartilage and soft tissue damage while providing good hemostasis. Endoscopic laryngotracheoplasty, with stenting for 1 to 2 weeks, may decrease operative time and morbidity when compared with open reconstruction.

ACKNOWLEDGMENTS — The authors thank Jeff Manni of JM Associates and William M. Hamilton of the Department of Anatomic Pathology, Lahey Clinic Medical Center, for their invaluable assistance.

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NORMAL AND ABNORMAL GROWTH AT THE NASOSEPTOVOMERAL REGION

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The purpose of this report is to review and summarize a selected series of previously reported experiments at the nasoseptovomeral region dealing with both normal growth and the effects of certain operative procedures in young and adult rabbits. The methods of study included gross and serial cephalometric radiography with radiopaque implants, histology, and autoradiography. Findings indicated that the frontonasal suture region was an active secondary site of growth unaffected by extirpation. Examples of differential sutural growth were presented. The proximal and distal regions of both the nasal bone and septum were their most active sites of growth. Extirpations of the central section of the cartilaginous nasal septum resulted in severe upper facial deformity in young but not in adult rabbits. Trauma to the nasal bone region in the young rabbit did not result in severe facial deformity as did trauma to the cartilaginous nasal septum. Another purpose of this report is to present some of the different approaches used to study the nasoseptovomeral region.

KEY WORDS — growth, nose, septum, surgical experimentation, vomer.

INTRODUCTION AND PURPOSE

As a surgeon I have been faced with questions in my clinical practice about normal growth and the effects on normal growth of surgical procedures at the nasoseptovomeral regions. For instance, what is the growth pattern of the nasal bone? What role does the frontonasal suture play? What is the differential cellular activity of the cartilaginous nasal septum? What are the effects of 1) acute dislocation of the cartilaginous nasal septum, 2) differential resection of the cartilaginous nasal septum, and 3) extirpation of the frontonasal suture? In an attempt to find some answers to these and other questions, specific basic science laboratory experiments were designed and performed. Because the literature is sparse on this particular subject, a selective organized review and summary of personally conducted experiments is timely. The reader is referred to earlier publications for details. The following will be considered in terms of normal growth: growth at the frontonasal suture,[1,2] the growth pattern of the nasal bone region,[3] and the differential cellular activity of the cartilaginous nasal septum.[4] I will also describe the effects of trauma in young rabbits: effects of acute dislocation of the cartilaginous nasal septum,[5] effects of resection of central linear segments of the cartilaginous nasal septum,[6] effects of resection of major amounts of the septovomeral region and/or cartilaginous nasal septum,[7-9] and effects of extirpation of the frontonasal suture region,[10] and in adult rabbits, the effects of resection of major amounts of the cartilaginous nasal septum[11].

NORMAL GROWTH

GROWTH AT FRONTONASAL SUTURE

The contribution to the growth of the face and snout of the frontonasal suture was studied in 25 young female New Zealand albino rabbits.[1,2] The method employed was that of operatively exposing the suture and inserting dental amalgam into a prepared 1-mm cavity in both the frontal and nasal bones (Fig 1[2]). The distances between the paired implants and from each implant to the suture were measured. At the end of the experimental period (5 days to 12 weeks) the animals were killed painlessly, the skulls dissected, and the same measurements repeated. In addition, serial ventrodorsal cephalometric radiographs were taken in a specially de-

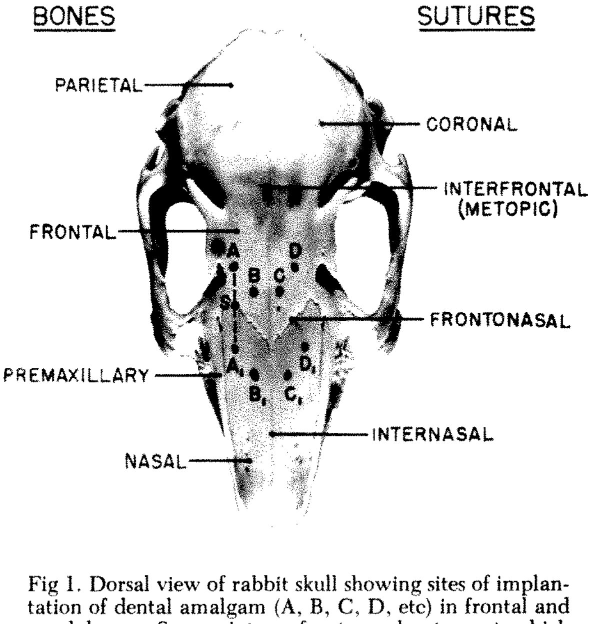

Fig 1. Dorsal view of rabbit skull showing sites of implantation of dental amalgam (A, B, C, D, etc) in frontal and nasal bones. S — point on frontonasal suture at which straight line crosses between A and A1, etc. (Reprinted with permission.[2])

From the Research Institute, Cedars-Sinai Medical Center, and the Section of Oral Biology, School of Dentistry, the Division of Plastic Surgery, School of Medicine, and the Dental Research Institute, University of California, Los Angeles, California. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of California.

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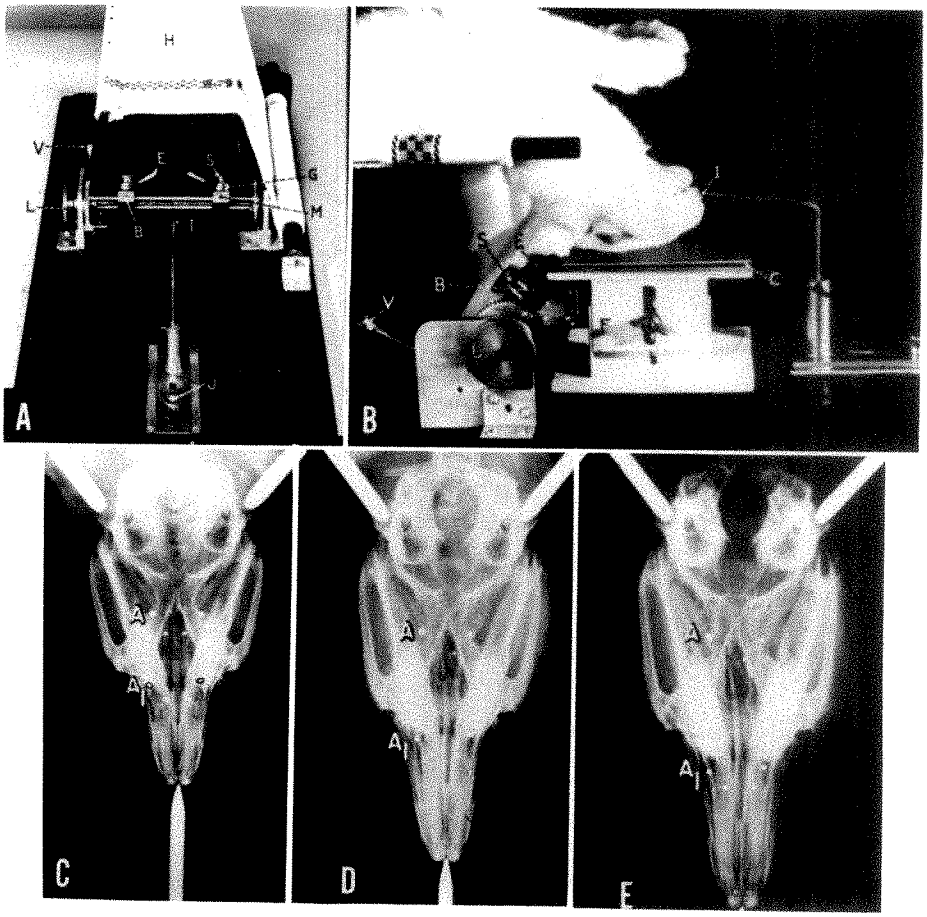


Fig 2. A,B) Views of headholder. B — earpost-bearing block, E — earpost, I — incisal pin, L — horizontal block-moving gear, S — earpost setscrews. A) Empty headholder. H — hammock, V — vertical rotating gear, G — earpost guide line, M — earpost-bearing block guide line, J — incisal pin slide-screw. B) Rabbit head in position on cassette with earpost in external ear. C — film cassette, F — film elevator. C-E) Ventrodorsal cephalometric radiographs. Note change in form of skull, and increased longitudinal and lateral separation of implants on either side of frontonasal, internasal, and interfrontal sutures. Distance between implants within nasal or frontal bones, however, remained constant. Tips of earposts are in external auditory canals. Incisal pin is in position. A, A1 — sites of implantation of dental amalgam. C) Six weeks of age. D) Ten weeks of age. E) Sixteen weeks of age. (Reprinted with permission.[1])

signed headholder (Fig 2A,B[1]) immediately upon completion of the procedure and at 14-day intervals (Fig 2C-E). From these radiographs the increased separation of the radiopaque amalgam implants could be determined for specific periods.

The increased distance between paired implants on either side of the frontonasal suture varied with the age of the animal at the time of implantation, the duration of the experiment, and the individual characteristics of the animal. Thus, in 42-day-old rabbits, the increased amount of separation of the implants after 7 days ranged from 0.3 to 1.3 mm. In another group of rabbits, the increased separation of the implants during an 84-day period (42 to 126 days of age) ranged from 10.6 to 11.9 mm. The mean increment of growth from 42 to 56 days of age was about 3.0 mm, and from 140 to 154 days it was only 0.3 mm. Thus the findings revealed that 1) there was increased separation of the implants at the frontonasal suture, 2) the rate was inverse to the increase in age, and 3) the nasal bone contributed about 65% and the frontal bone contributed about 35% at the frontonasal suture to the separation of the implants.

At the internasal and interfrontal sutures the total amount of growth of bone was estimated to be about one 10th to one 20th that at the frontonasal suture. The changes in proportion of the snout were determined by 1) the number of growth sites in a given direction, 2) the rate of bone deposition at a given site, and 3) the length of time over which growth at that site was active.

GROWTH PATTERN OF NASAL BONE REGION

Differential growth activity at several borders of the nasal bone region was studied.[3] Two radiopaque implants were inserted into each left and right nasal bone in five young female New Zealand albino rabbits. Ventrodorsal cephalometric radiographs were obtained in a specially designed headholder when the rabbits were 6 and 16 weeks of age. From these radiographs separate tracings were made on matte acetate paper of the left and right nasal bone regions, including the radiopaque implants. Since the implants maintained the same relation to each other in each nasal bone, they served as stable reference sites. The markers of the 16-week tracing were superposed on the markers of the 6-week tracing (Fig 3[3]). The difference in the two established outlines represented the changes in size and shape in two dimensions that had occurred during the 10-week period. The mean increase was about 6.79 mm at the proximal (posterior) border, 6.19 mm at the distal (anterior) border, 2.73 mm at the lateral border, and 1.22 mm at the medial border. Thus, growth at the proximal and distal borders was approximately equal and about twice that of the lateral border and

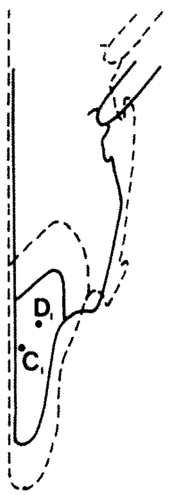


Fig 3. Tracings of left nasal bone region at 6 weeks of age (solid line) and 16 weeks of age (broken line), taken from ventrodorsal cephalometric radiographs and superposed on implant images. Note growth pattern of nasal bone region, with greatest increase in size proximally and distally, less laterally, and least medially. C1, D1 — implant tracing. (Reprinted with permission.[3])

about five times that of the medial border.

DIFFERENTIAL CELLULAR ACTIVITY OF CARTILAGINOUS NASAL SEPTUM

Autoradiographic studies with tritiated thymidine were undertaken to determine normal levels of proliferative activity in the rabbit cartilaginous nasal septum of a 3-week-old Dutch rabbit.[4] It was given a single intraperitoneal injection of 258 μCi of tritiated thymidine and killed painlessly 1 hour later. The head was divided parasagittally and fixed in Hollande's modification of Bouin's fluid. The cartilaginous nasal septum region (Fig 4[7]) was embedded in paraffin. Parasagittal sections were cut 6 μm thick and autoradiographed.

A complete section approximating the midline was selected for intensive microscopic study. Under oil immersion (1,000 diameters) the field of view was subdivided by use of an ocular grid, and all labeled and unlabeled nuclei within successive fields were counted. Regional zones of the specimen were defined arbitrarily, and labeling indexes were determined for each region (Fig 5[4]). Cell counts in some regions were made on a limited sampling basis, but always included 1,000 or more nuclei to provide an adequate basis for comparison with other regions. A total sample of 78,125 cells, 1,031 of which were labeled, was observed in the specimen.

The posterior aspect of the septum is directly contiguous with the endochondral growth site of the septoethmoidal junction; so the increased proliferative activity in zones 2, 3, 6, 8, and 9 may reflect endochondral growth in this region. Endochondral ossification, however, did not occur at the anterior and anteroinferior aspects of the septum (zones 1, 4, 5, 7, and 11), in which comparably elevated proliferative activity was also observed.

Active differential proliferation of the cellular component of the cartilaginous nasal septum was noted in the growing rabbit, and this proliferation was most pronounced in the anteroinferior and posterior zones. The increase in cellular mass presumably contributed to the growth of the cartilaginous nasal septum as a whole.

EFFECTS OF TRAUMA IN YOUNG RABBITS

EFFECTS OF ACUTE DISLOCATION OF CARTILAGINOUS NASAL SEPTUM

In this group of 10 New Zealand albino rabbits 5

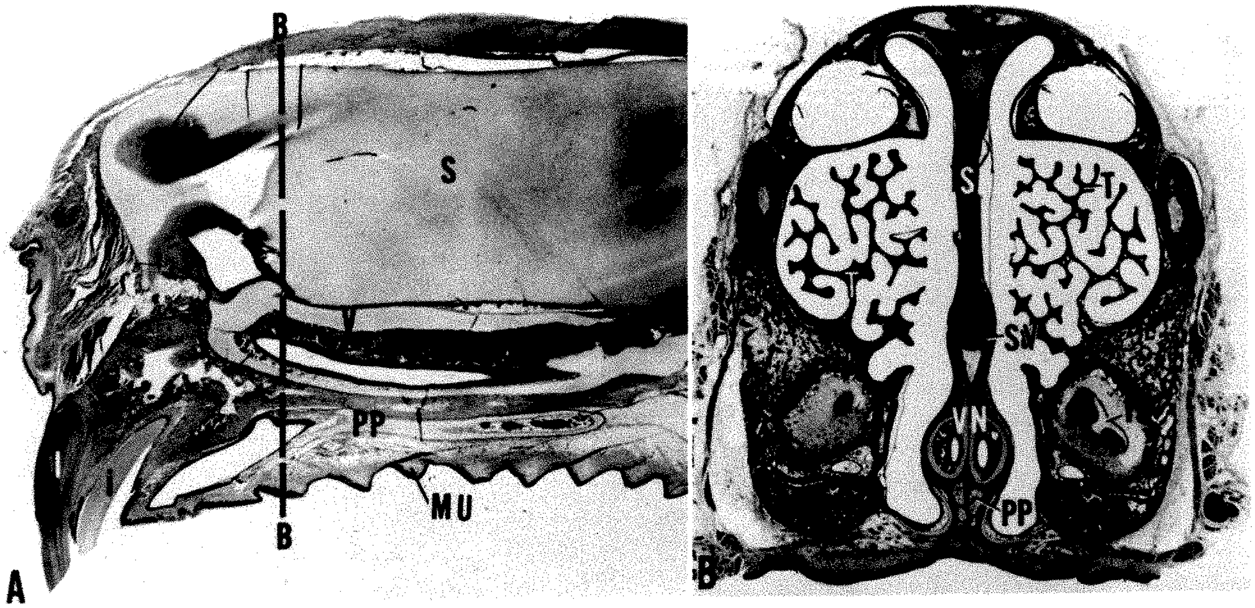


Fig 4. Photomicrographs of A) sagittal and B) transverse (taken at about line B-B) sections of snouts of 28-day-old unoperated-on rabbits (original x6). I — labial incisor, i — lingual incisor, IB — basal end of incisor, MU — palatal mucosa, PP — palatine process of premaxilla, S — septum, SV — septovomeral joint, T — maxilloturbinate, V — vomer, VN — vomeronasal organ. (Reprinted with permission.[7])

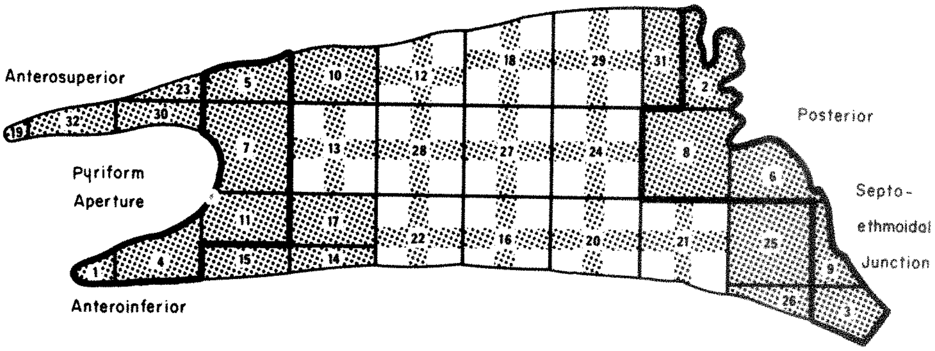


Fig 5. Diagrammatic representation of longitudinal section of cartilaginous nasal septum of 3-week-old Dutch rabbit after intraperitoneal injection of tritiated thymidine. Various zones are numbered according to their relative activity (labeling index: zone 1, 3.36%; zone 32, 0.35%). Anteroinferior and posterior areas (heavily outlined) were most active. Cell counts were made of stippled areas. (Reprinted with permission.[4])

to 7 weeks of age, the inferior border of the cartilaginous nasal septum was mobilized by lifting it out of the vomerine groove and completely dislocating it laterally.[5] No tissue was resected. The postoperative survival time was 16 weeks.

External gross examination of the snout, upper and lower jaws, and teeth disclosed no significant differences between the operated-on and unoperated-on animals. Examination of the transversely sectioned snouts revealed that the dislocated septal cartilage returned to its normal position or close to it, so that continuity from the floor of the snout to the dorsum was reestablished (Figs 4 and 6[5]). In some instances lateral deviation and deformity of the septum and vomer were noted.

EFFECTS OF RESECTION OF LINEAR SEGMENTS OF CARTILAGINOUS NASAL SEPTUM

In six New Zealand albino rabbits 3 weeks of age, central septal cartilage and mucous membrane sections ranging from 3 to 6 x 9 to 15 mm were resected with preservation of the surrounding borders.[6] The postoperative survival time was 16 weeks.

Antemortem, a lack of forward growth of the upper face, sometimes associated with overeruption and malocclusion of the incisors, was noted within 6 weeks in some of the experimental animals. The findings, although less extreme, were similar to the findings in the animals with more extensive resection of cartilaginous nasal septum.

Postmortem, in some animals, no or little septal defect was noted on cursory examination. Upon further study, however, and after the overlapping margins of the septum were retracted, the true extent of the septal defect could be evaluated. The segment of cartilage resected was about 5 x 9 mm. At the time of death the size of the defect was about 3 x 16 mm. This difference raised the question of the role of the growing and expanding nasal septal cartilage upon growth of the snout. After the window was made, apparently the cartilage continued to grow, but its expansive interstitial force was dissipated in this region, and the overlap resulted.

EFFECTS OF RESECTION OF MAJOR AMOUNTS OF SEPTOVOMERAL REGION AND/OR CARTILAGINOUS NASAL SEPTUM

In 59 New Zealand albino rabbits 2 to 7 weeks of age, major amounts of the septovomeral region and/or cartilaginous nasal septum were resected.[7-9] The postoperative survival time ranged from 1 to 21 weeks.

Antemortem Observations. As early as 4 days after resection of the cartilaginous nasal septum, there was a reversal of the relationship of the incisors, with the upper ones being lingual to the lower. Subsequently, the sharp incisal edge on the labial surface was not maintained. In the experimental animals with a longer postoperative survival, considerable overeruption and fractures of the incisors were frequent. At times food would become lodged be-

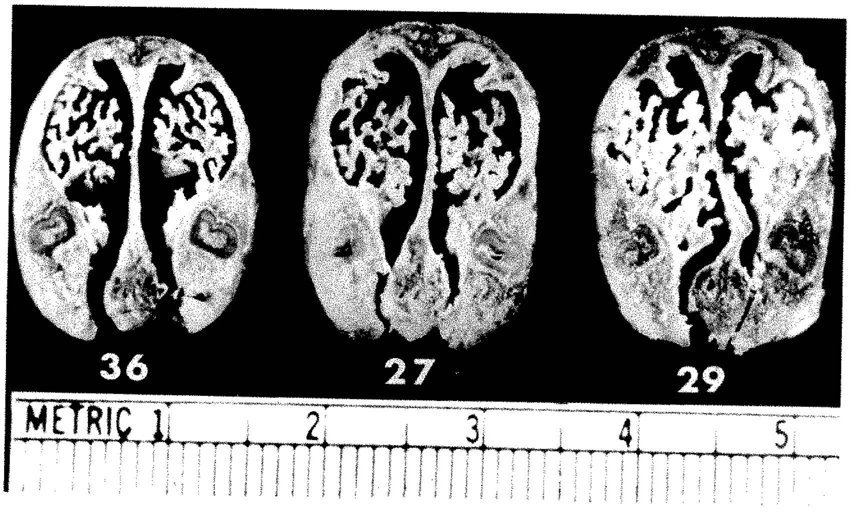


Fig 6. Postmortem photographs of transverse sections of rabbit snouts at level of basal end of incisors of rabbit 36 (unoperated-on control) and rabbits 27 and 29, in which septum was dislocated laterally. Note lateral deviation of septum in No. 27, and more extreme deformity of septum and vomer in No. 29. No external deformity of snout was noted. (Reprinted with permission.[5])

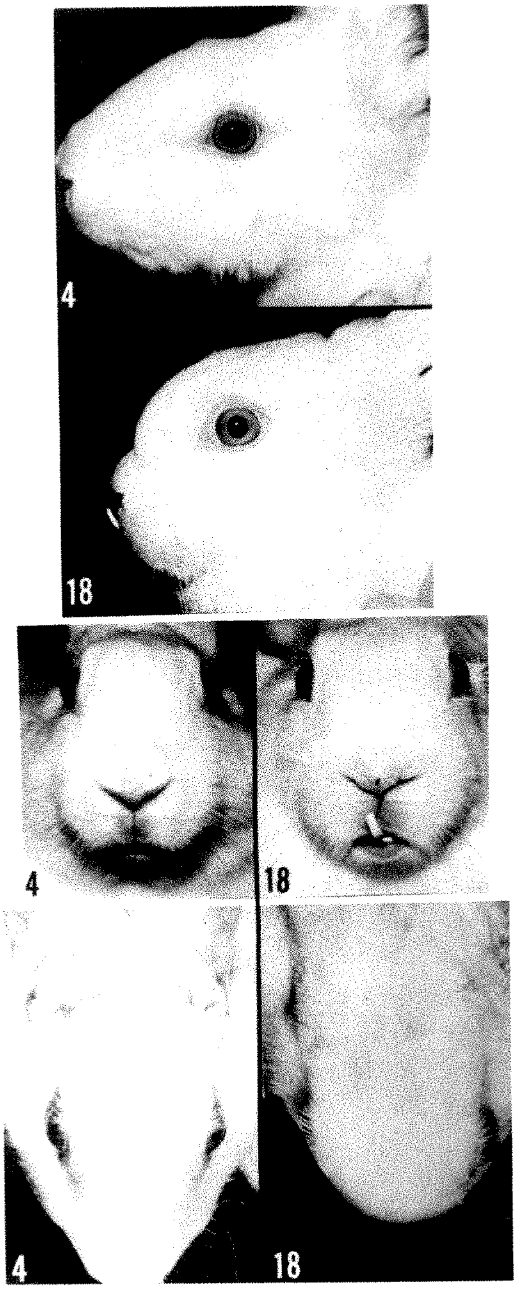


Fig 7. Antemortem lateral, frontal, and dorsal (retouched) photographs of littermate rabbits. Major amount of nasal septum was removed at 21 days of age from No. 18. Note contrast in facial appearance. Animal 4 has relatively normal, long, tapered face, whereas animal 18 has short, stubby, rounded face with indentation above nostrils (lateral view) and overerupted lower incisor. (Reprinted with permission.[8])

tween the spread incisors. These factors sometimes made ingestion difficult. In a few of the experimental animals the weight was less and the fur was not as smooth as in the controls.

The long, smoothly curved, tapered face seen in the operated-on and unoperated-on control animals was in considerable contrast to the face of the experimental rabbit (Fig 7[8]). The snout became progressively stubby with postoperative survival, along

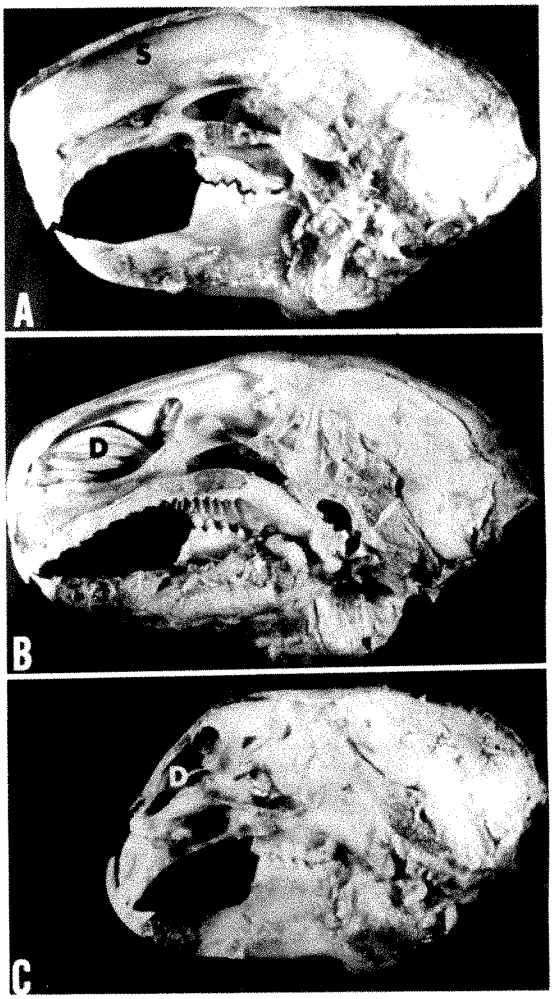
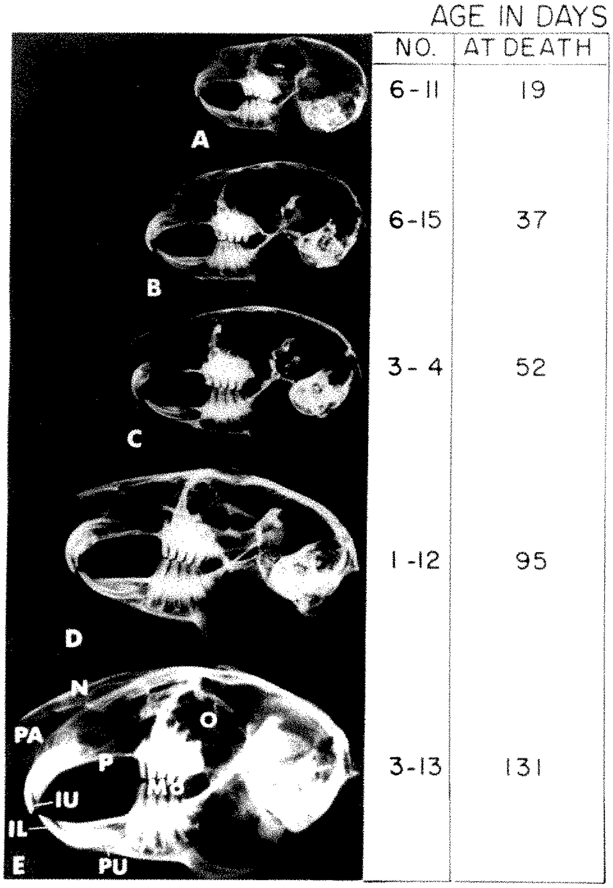


Fig 8. Postmortem photographs of right halves of left parasagittally sectioned rabbit skulls. A) Operated-on control animal. None of cartilaginous nasal septum (S) was resected. B) Cartilaginous nasal septum was resected in this experimental animal when it was adult. Compare with A and note similarities of size, shape, and regularity of incisors. Also note regularity of dorsal curvature uninfluenced by underlying septal defect (D). C) Cartilaginous nasal septum was resected in this experimental animal at 3 weeks of age, and animal was killed at about 4 months of age. Note growth arrest of snout and malocclusion of incisors. Also note deflection of snout in anterior direction beginning in region of septal defect (D). (Reprinted with permission.[11])

with the appearance of a pronounced indentation above the tip of the nose. This was suggestive of the face of a bulldog and was prominent within 3 weeks postoperatively.

Postmortem Observations. Changes noted in the dissected skulls of the experimental animals were limited to the snout in the region anterior to the orbits, zygomas, and molars. Although the findings were not always consistent, generally the degree of change varied directly with the amount of septum resected and the postoperative survival period.

The following description is characteristic of the most severe deformities seen in animals with the longest postoperative survival. The snout, when

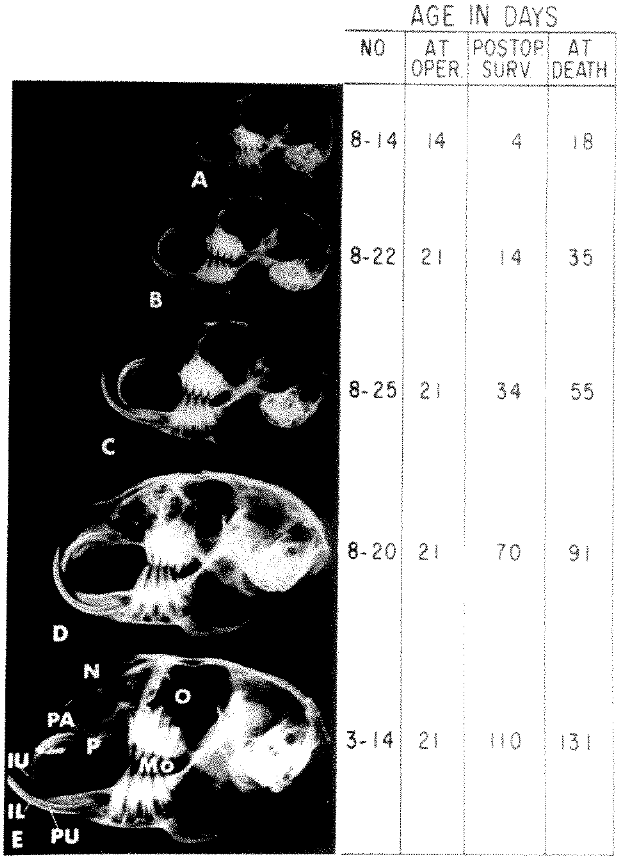


AGE IN DAYS	
NO.	AT DEATH
6-11	19
6-15	37
3-4	52
1-12	95
3-13	131

Fig 9. Reproduction of lateral radiographs, arranged according to age from 19 to 131 days at death (A-E), of parasagittally sectioned skulls of rabbits with cartilaginous nasal septum intact. Note downward smooth curve of anterior dorsum; length and anterior extension of nasal bone; size of pyriform aperture; length of palate; and form, position, and relationship of incisors. Contrast these with experimental animals in Fig 10. IM — lower incisor, IU — upper labial and lingual incisors, Mo — premolars and molars, N —nasal bone, O — orbit, P — palate, PA — pyriform aperture, PU — pulpal cavity. (Reprinted with permission from Sarnat BG, Wexler MR. Longitudinal development of upper facial deformity after septal resection in growing rabbits. Br J Plast Surg 1969;22:313-23.)

seen from the side, was tapered and less long than that of the unoperated-on control (Fig 8[11]). Whereas the snout in the control animal was the prominent part of the anterior face, this was not so in the experimental rabbit. There was a considerable deflection of the snout in a forward direction, beginning anterior to the frontonasal suture. This was in contrast to the smoothly curved dorsum of the control animals. From below, the palate and the incisive foramen were less long. From in front, the nasal aperture was less large. The snout when viewed from above was considerably less long than that of the littermate control animal.

The nasal bones were considerably less long and narrower than those of the control animals and converged toward the premaxilla, with nasal height and volume considerably less. The premaxilla and its frontal process were also less long. The end of the snout was tapered in the dorsoventral direction.



AGE IN DAYS			
NO	AT OPER.	POSTOP SURV	AT DEATH
8-14	14	4	18
8-22	21	14	35
8-25	21	34	55
8-20	21	70	91
3-14	21	110	131

Fig 10. Reproduction of lateral radiographs, arranged according to postoperative survival, of parasagittally sectioned skulls of rabbits that had cartilaginous nasal septum resected at 14 or 21 days of age with postoperative survival of 4 to 110 days. Note flat anterior dorsum with increasing downward deflection in anterior direction with increasing postoperative survival. Deflection begins at posterior site of resection. Contrast these with control animals in Fig 9. Note less long snout, nasal bone, and palate and less large pyriform aperture. Also note in A that upper incisal edge is just lingual to lower one. This is more extreme in animals with longer postoperative survival (B-E). Also in contrast with Fig 9, incisors are considerably overerupted and longer and not in occlusion. IU — upper incisor. Other abbreviations as in Fig 9. (Reprinted with permission from Sarnat BG, Wexler MR. Longitudinal development of upper facial deformity after septal resection in growing rabbits. Br J Plast Surg 1969;22:313-23.)

Examination of the parasagittally sectioned crania revealed in the experimental animals the extent of the septal defect in relation to the remaining septum and deformity of the snout, and in the control animals, the relation of the extent of the nasal septum to the snout. The site of the beginning of the downward deflection of the nasal bones was correlated with the posterior border of the septal defect, which was anterior to the frontonasal suture (Fig 8). Whereas in the control animal the nasal bones and hard palate were about parallel, in the experimental animal anterior projections of lines from the surfaces of these bones would soon intersect.

The upper incisors were usually in lingual occlusion with the lower incisors — the reverse of normal. The upper and lower incisors were overerupted, in considerable malposition, fractured, and deviated (Figs 8C and 10). The sharp labial bevel was frequently absent or reversed.

RADIOGRAPHIC OBSERVATIONS

Examination of the radiographs of the parasagittally sectioned skulls revealed findings not seen on the gross specimens. Differences between the control (Fig 9) and experimental (Fig 10) animals were demonstrated in the lateral radiographs of the parasagittally sectioned skulls. Comparisons were significant not only between the two groups but also within each group with increase in the postoperative survival period.

In the experimental animals the anterior dorsum of the skull was flat in the younger animals. With increase in postoperative survival this region was relatively less long, more posterior, and closer dorsoventrally to the upper incisors than in the control rabbits. Other findings in the experimental animals were larger pulpal cavities in the incisors, an increase in the proportion and amount of erupted compared to unerupted incisors, and lesser amounts of alveolar bone supporting the incisors.

EFFECTS OF EXTIRPATION OF FRONTONASAL SUTURE REGION

The purpose of this experiment was to study the effects of trauma on the frontonasal suture, a site of active growth.[10] Extirpation of the suture was imposed upon 28 female New Zealand albino rabbits 42 to 48 days of age. A dental bur mounted in a handpiece was used to extirpate the frontonasal suture region either unilaterally or bilaterally. About a 1-cm channel was cut equally from both the frontal and nasal bones.

Dental amalgam was packed into prepared cavities 0.5 to 1.0 cm from the channel edge. On a line between the frontal and nasal bone implants the following measurements were made: the distance between the two implants, the distance of each implant from its adjacent channel border, and the width of the channel. Immediately upon completion of the procedure, a ventrodorsal cephalometric radiograph was taken. This was repeated at 14-day intervals. The 14-day increments and total amount of increased separation between implants in the frontal and nasal bones, after either bilateral or unilateral extirpation of the frontonasal suture, were studied. Postoperative survival ranged from 14 to 84 days. The distances between the implants and extirpation borders were determined directly at the beginning of the experiment as well as at death.

The gross size and shape of the snout in the rabbits in which the frontonasal suture had been either bilaterally or unilaterally extirpated was similar to that of the control rabbits. No lateral deviation of the snout was observed in the rabbits with a unilateral extirpation. A less long snout was not seen in the rabbits after bilateral extirpation of the frontonasal suture. Rather, it was found that total longitudinal growth was essentially the same in both the control animals and those animals in which the suture was either bilaterally or unilaterally extirpated. With respect to the increased separation of the implants, the nasal part of the frontonasal suture contributed about half, the extirpation site a fourth, and the frontal part a fourth. The channel width increased as longitudinal growth proceeded. Thus, a wedging or expansive force between the frontal and nasal bones by the frontonasal suture apparently was not necessary for growth in that region. Separation of the nasal and frontal bones, in the absence of the normal suture, continued at all times in an amount not significantly different from normal.

One concept of sutural bone growth describes it as an expansion initiated by a proliferation of the sutural connective tissue. The separation of the contiguous bones is said to be followed immediately by apposition of immature bone along the contiguous borders. These studies indicated that extirpation of a facial suture failed to produce a growth arrest. Thus, although a suture is a site of active growth, it is secondary to some factor other than primary growth.

EFFECTS OF RESECTION OF MAJOR AMOUNTS OF CARTILAGINOUS NASAL SEPTUM IN ADULT RABBITS

Questions arose as to the role of the cartilaginous nasal septum and its sites of activity in relation to growth and form of the snout. Is the snout deformity a result of lack of growth of the cartilaginous nasal septum or lack of support? Thus, in nine adult New Zealand albino rabbits major amounts of cartilaginous nasal septum were resected.[11] The postoperative survival time was 16 weeks.

Antemortem observations of the snout and incisors revealed no gross differences between the control and experimental rabbits. Postmortem gross examination of the lateral and parasagittal views of the face, jaws, and incisors likewise showed no special differences between the control and experimental rabbits. Inspection of the right half of the left parasagittally sectioned skulls disclosed a large defect of the cartilaginous nasal septum in the experimental animals (Fig 8B). No unusual deflection of the nasal bones was noted.

COMMENTS

Findings in experimental animals may be of assistance in understanding normal and abnormal growth in the human being. Deformities of the nasal septum and associated structures seen clinically in the adult have been considered manifestations of severe injury incurred during an earlier period.

The rabbit was selected because of the rapid growth of its snout. The amount of increase in separation of the implants on either side of the frontonasal suture indicated that this was a site of considerable growth. Information was obtained about total amount, rate, and direction of bone growth and highlighted periods of maximum and minimum growth activity at a particular time. Many instances of differential sutural growth were demonstrated. Of particular interest was the finding that the nasal side of the frontonasal suture contributed about twice as much as the frontal side to growth of that suture.

Growth at this region was not affected after resection of the frontonasal suture. Thus, it was concluded that the frontonasal suture was a secondary growth site. Since severe trauma to this growth site did not result in a deformity, the information may be relevant in regard to the nasal bones when either a fracture occurs or an osteotomy is performed as part of a rhinoplastic procedure in a child or adolescent. Providing that the nasal bones are repositioned satisfactorily, no deformity should result. The proximal (frontal) end of the nasal bone in rabbits is the most prolific of the nasal bone growth sites.

In contrast, resection of the cartilaginous nasal septum in young rabbits produced a severe and striking deformity involving a less large snout. One interpretation to consider is that the growing cartilaginous nasal septum in rabbits is a primary and important growth site of the snout and the upper portion of the face. Thus, what are the effects of resection of cartilaginous nasal septum upon growth at the frontonasal suture?

Trauma to the nasal septum in children can result in severe deformity. It would be advisable that children who have sustained injuries to the cartilaginous septum and nose be treated and observed not only for immediate effects but also for later septal and nasal deformities. In a child with a complete bilateral cleft palate, the upper face may be unable to obtain a full expression of downward and forward growth because of lack of contact of the palatal shelves with the ventral-free, actively growing septovomeral region. Furthermore, trauma to the septal region during surgical procedures on a cleft palate or on the septum might have an untoward effect upon growth of the nose and upper jaw and face.

Does growth of the nasal septum drive the snout forward, with sutural accommodation of the related bones? Did resection of a large part of the septum trigger closure, cessation, or decrease of activity of the suture complex in the growing nasal bone region? Does normal interaction of the various growth patterns in a bone complex require maintenance of normal spatial relations of the individual units in the complex? Further investigation such as a study of frontonasal sutural growth after septal resection is indicated.

An understanding of normal and abnormal postnatal skeletal changes and lack of change in both young and adult animals can aid in the prevention, early recognition, and improved surgical and nonsurgical treatment of nasoseptovomeral deformities. There are also methods other than those described here to study growth of this region.[12] Research findings may have important implications and applications in relation not only to the basic problem of change of bone form, but also to the clinical problems of nasoseptovomeral procedures.

ACKNOWLEDGMENT — I am grateful to Lori Goldman and the Word Processing Center at UCLA for devoted assistance in the preparation of this article.

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Ann Otol Rhinol Laryngol 100:1991

IMAGING CASE STUDY OF THE MONTH

INFRATEMPORAL FOSSA ABSCESS

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IOWA CITY, IOWA

PATIENT

A 19-year-old man presented with a 3-day history of dull, throbbing pain in his right upper molar region. The patient had been seen by a dentist 2 days prior to admission, when an abscess was found in tooth 3 and treated with a pulpectomy, postoperative ampicillin, and analgesics. No cultures were performed. The patient returned the next day because of increased swelling and pain and underwent an incision and drainage of a right buccal space abscess with placement of a drain.

The patient presented the following day with a complaint of progressive pain and swelling of his right upper jaw, trismus, and decreased visual acuity in the right eye. On examination the patient was in moderate distress with swelling over the right side of the hard palate, the right upper buccal vestibule, and the right temporal space. No fluctuance was appreciated and the right buccal space drain was in place without drainage. The patient was afebrile and vital signs were normal. The white blood cell count was 7,700 with a normal differential.

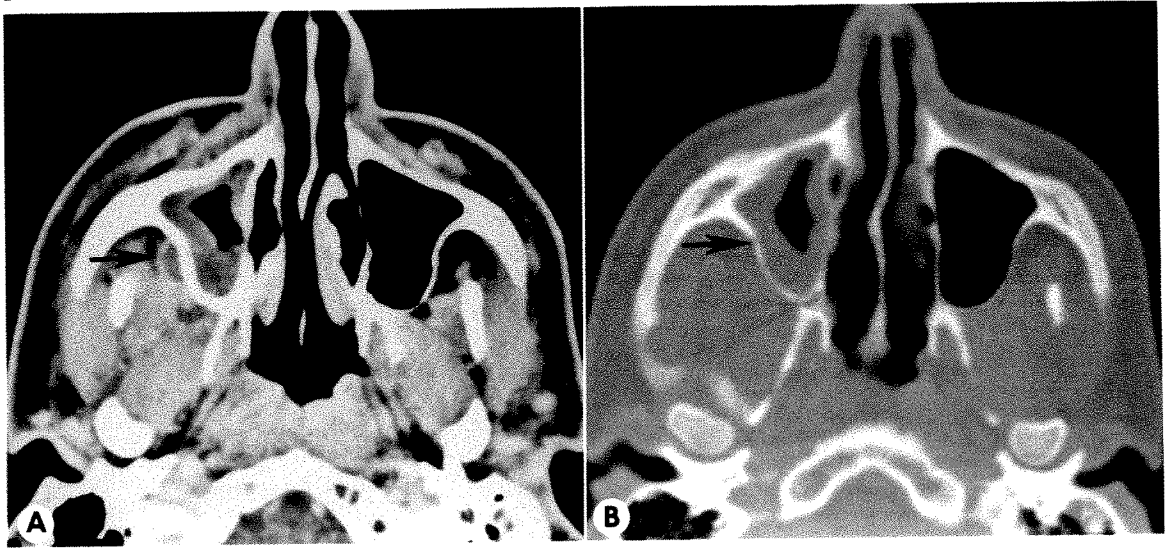
RADIOGRAPHIC FINDINGS

A plain sinus series revealed an opacified right maxillary sinus and malar soft tissue swelling. Axial computed tomography (CT) revealed soft tissue thickening on a soft tissue window view (see Figure, A). The normal retromaxillary fat accumulation was increased in density, indicating edema. Along the posterolateral surface of the maxillary wall an area of enhancement is present and represents the maxillary wall periosteum. This area of enhancement surrounds a low-density area consistent with pus. Anteriorly, edema produces thickening of the muscles of facial expression.

A bone window representation of the same area (see Figure, B) shows a "notch" in the bone wall that represents a cross section of the posterior superior alveolar neurovascular canal near its origin.

HOSPITAL COURSE

The patient was treated with intravenous gentamicin sulfate and Cleocin, Afrin nasal spray twice daily, and analgesics as needed. The patient showed steady improvement with normalization of visual acuity within 24 hours and decreasing pain, swelling, and trismus over the next several days. The drain was pulled on the third hospital day and the



Axial midmaxillary computed tomograms. A) Showing right-sided mucosal thickening of sinus. Right retromaxillary fat has increased density produced by edema. Centrally along posterolateral sinus wall, area of enhanced periosteum is displaced by pus (arrow). B) Bone window view of same area depicted in A showing notch (arrow) that represents posterior superior alveolar neurovascular canal that lies in center of abscess shown in A.

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patient was discharged on the fifth hospital day on a regimen of Cleocin (150 mg orally four times daily) and analgesics. The patient was without complaint when seen at 1 week follow-up.

DISCUSSION

Abscesses involving the infratemporal fossa have been seen secondary to maxillary sinus fracture and infections involving the maxillary molars.[1,2] The posterior wall of the maxillary sinus forms the anterior boundary of the infratemporal fossa and contains alveolar canals through which run the posterior superior alveolar nerves and vessels. These canals provide an avenue for infection from the maxillary sinus or upper molars to the infratemporal fossa. The proximity of the pterygoid plexus to the infratemporal fossa creates a potential for spread of infection to the cavernous sinus via the foramen Vesalii, foramen ovale, and foramen lacerum. In addition, orbital complications could evolve from spread of infection through the valveless ophthalmic veins that anastomose with the pterygoid plexus.

Infratemporal space abscesses are difficult to evaluate on plain films but are readily apparent on CT evaluation. The loss of the retromaxillary fat plane is a most notable feature. *Streptococcus* spp and *Bacteroides* spp have been isolated from these abscesses. Therapy consists of incision and drainage, appropriate antibiotic therapy, and debridement of necrotic bone in the case of maxillary sinus fractures.

Trismus in association with increasing pain and swelling in the upper jaw may be secondary to inflammation around the temporalis and internal and external pterygoid muscles and should lead to suspicion of an infratemporal space abscess. Axial CT is sensitive in detecting abscess of the infratemporal fossa and should be used when this lesion is suspected.

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IMAGING CASE STUDY OF THE MONTH

CYSTIC HYGROMA OF THE PAROTID GLAND

KERSTIN M. STENSON, MD
JOSEPH MISHELL, MD
DEAN M. TORIUMI, MD
CHICAGO, ILLINOIS

CASE REPORT

The patient is a 9-year-old boy who had a slowly enlarging mass of the left parotid region since birth. There was no fluctuation in size, nor was there a history of pain, inflammation, or facial weakness. After observing the patient for 6 years, we noted that the mass began to increase in size and became cosmetically deforming. On physical examination, the patient had a soft, fixed, nontender 6 x 5-cm cystic mass in the left parotid region.

Computed tomography (CT) revealed an oval-shaped mass superficial to the left parotid gland, although the inferior margin of the mass was difficult to distinguish from parotid fascia. A magnetic resonance imaging (MRI) scan was done to determine if the mass infiltrated the gland and what was the relation of the mass to the facial nerve. This information was critical to determine if a facial nerve dissection would be required to surgically excise this benign tumor.

The MRI revealed a well-defined mass below the infratemporal region that involved both the superficial and deep lobes of the left parotid gland. The T1-weighted images showed a low-intensity signal, while T2-weighted images revealed a high-intensity signal (see Figure, A). The facial nerve could be seen traversing the mass on T2-weighted images (see Figure, B). The mass was superficial to the masseter and platysma. The MRI findings of a cystic lesion containing proteinaceous fluid were consistent with a cystic hygroma infiltrating the left parotid gland. With this information, we obtained informed consent for total parotidectomy and facial nerve dissection, emphasizing the risk of left facial nerve paresis or paralysis.

Through a rhytidectomy incision the mass was noted to infiltrate the entire gland. The patient underwent a left total parotidectomy with facial nerve dissection. The mass was multiloculated and involved both the superficial and deep lobes of the gland. The facial nerve branches passed between the multiple loculations of the mass. The temporal and zygomatic branches of the facial nerve were splayed around the mass, making dissection of the distal segment of these nerves very difficult. The final pathology report was consistent with parotid lymphangioma. Postoperatively, the patient demonstrated paresis of the temporal branch of his left facial nerve. The paresis completely resolved within 2 months. There was no evidence of tumor recurrence after a follow-up period of 12 months.

DISCUSSION

Cystic hygromas or lymphangiomas are considered to be benign congenital neoplasms derived from abnormalities in the development of the lymphatic system. The neck is the most common site of involvement, with 50% to 65% presenting at birth and 80% to 90% presenting before 2 years of age.[1] Cystic hygromas of the parotid gland are rare occurrences. Only two cases of parotid lymphangioma were found by Wright et al[2] in a 25-year retrospective study of surgical pediatric parotid diseases.

The most common site for lymphangioma in general is the neck, especially the posterior triangle.[3] The face, tongue, and floor of the mouth are also frequently involved.[4] Indeed, it is more common for cystic hygromas of the neck to *secondarily* involve the parotid gland. Of the salivary glands, the parotid is the most common site.[5]

Cystic hygromas of the parotid gland progressively enlarge with time and present as a painless, soft fluctuant mass that will transilluminate if not previously infected.[5,6] Most references describe occasional rapid increases in size of the mass associated with trauma, upper respiratory tract infection, or hemorrhage into the cysts.[5] Lingeman,[7] however, states that this behavior is more characteristic of the cervical type of lymphangioma.

In general, it is stated that between 15% and 70% of lymphangiomas will involute during the first 20 years of life.[8] However, most authors feel that spontaneous regression is infrequent, and although the cysts may decrease in size, they usually refill with fluid and enlarge over time.[5,7,9]

Complications associated with untreated cystic

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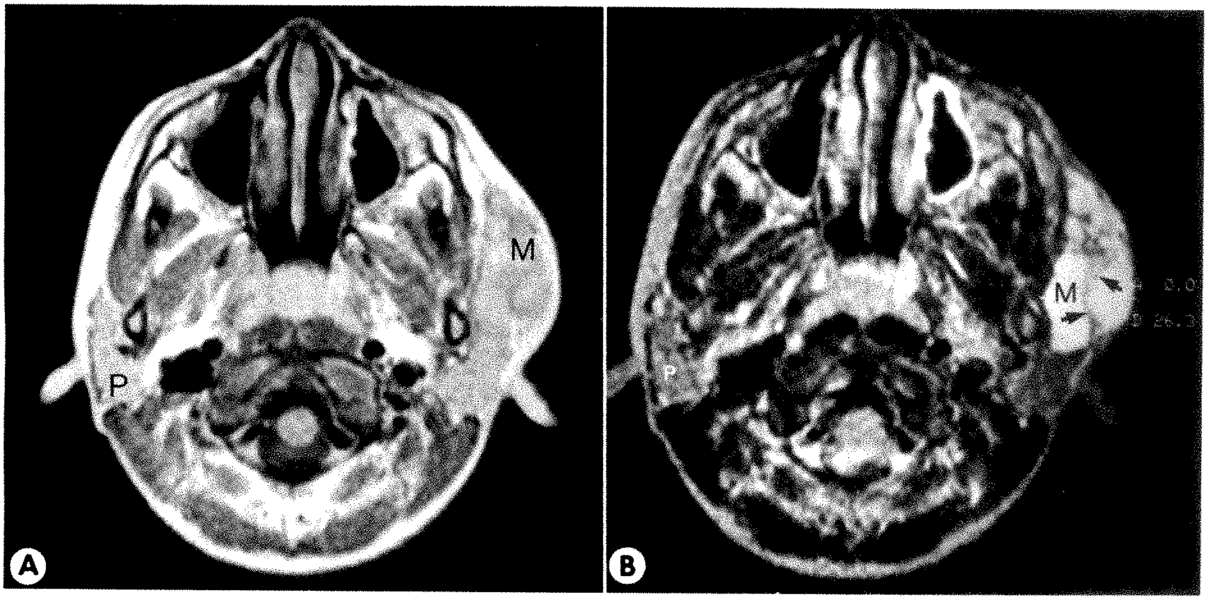

MRI scans. M — mass, P — right parotid. A) T1-weighted image, axial plane. Note low-intensity signal mass at left parotid region. Mass completely obliterates left parotid. B) T2-weighted image, axial plane. Note facial nerve traversing through high-intensity signal mass (arrows).

lymphangioma are related to the mass effect in the head and neck such as tracheal or esophageal compression.[5,9] Malignant change to lymphangiosarcoma has never been reported in primary parotid involvement or in head and neck lymphangiomas in general.[8,10]

Although definitive tissue diagnosis of parotid lymphangioma is best achieved with parotidectomy, several imaging studies may be useful in the preoperative evaluation. Aspiration of the mass contents is not recommended, since it may lead to hemorrhage and/or infection.[1,3,5,6] Ultrasonography will reveal multilocular cystic masses with ill-defined boundaries.[11] However, extension of the mass into deeper structures and the delineation of soft tissues are more accurately depicted by CT or MRI.[12] In this respect, MRI is superior to CT.

The advantages of MRI include 1) superior soft tissue discrimination, 2) the ability to better define the *extent* of a lesion, 3) multiplanar, potentially three-dimensional imaging, 4) lack of ionizing radiation, and 5) diminished need for use of intravenous contrast material.[13-15]

Magnetic resonance images of parotid lymphangiomas have a typical appearance.[12] The T1-weighted images reveal a heterogeneous, low-intensity signal similar to muscle, while T2-weighted images have a high-intensity signal greater than that of fat. These findings are characteristic unless the lesion has been complicated by hemorrhage, infection, or prior operation.[16] Because of their high protein content, hemangiomas have a similar appearance on MRI and can only be differentiated from lymphangiomas by demonstration of feeding arteries or draining veins.

The treatment of choice for cystic hygromas is surgical excision via parotidectomy with preservation of the facial nerve. Some authors suggest expectant management until the age of 3 to 5 years, at which time an operation may be undertaken if regression has not occurred.[4,8] Most authors, however, recommend parotidectomy whenever the diagnosis of cystic hygroma is made.[1,5,6] Expedient operative management is especially important in the parotid region, where repeated trauma and infection can make facial nerve dissection more difficult. Also, with progressive growth of the lesion, the chance of complete excision is decreased.[1]

Lymphangiomas have a recurrence rate of 10% to 15% within 1 year after excision.[3] Although residual lymphangiomatous tissue may fibrose, atrophy, or remain static, some authors feel that lymphangiomas of the parotid gland tend to recur if incompletely excised.[5,7,10]

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PATHOLOGY CONSULTATION

SUBLINGUAL GLAND

JOHN G. BATSAKIS, MD
HOUSTON, TEXAS

The smallest of the major salivary glands, the sublingual gland is unusually the origin of a salivary neoplasm. When it is, however, the odds are greatly in favor of the neoplasm's being malignant. The gland is also uniquely associated with two nonneoplastic disorders: the cervical ranula and herniation through the mylohyoid muscle.

The sublingual gland has several unique characteristics (Fig 1): the sublingual "complex" is the smallest of the major salivary glands; the gland has the highest ratio of malignant to benign tumors of any of the major and intraoral salivary gland tissues; it is claimed to be the source of cervical or plunging ranulas; and it is the most common tissue found in the mylohyoid boutonniere (sublingual bouton).

Of a mosaic composition, the sublingual gland is not a unit organ.[1,2] It comprises a large segment (the major sublingual gland) and a group of 8 to 30 small, independent, and aggregated glands (the minor sublingual glands).[2] The larger gland is drained by the sublingual duct (Bartholin's), with smaller ducts (ducts of Rivinus) draining the minor glands.[2] The sublingual complex is situated beneath the mucosa of the floor of the mouth at the side of the frenulum linguae, in contact with the inner aspect of the mandible, close to the symphysis. It is in relation below with the mylohyoid muscle; in front with the depression on the side of the symphysis and its fellow of the opposite side; behind with the deep part of the submandibular gland; and internally with the geniohyoglossus muscle, from which it is separated by the lingual nerve and Wharton's duct.

Ultrastructural observations by Riva et al[2] indicate the major component of the sublingual gland complex is a mixed salivary gland, with mucous cells slightly outnumbering seromucous cells. The larger mucous cells, however, occupy a much larger fractional volume. The mucous cells are arranged in lobules, with the seromucous cells most often situated as demilunes at the blind ends of the tubules. Compared to the parotid and submandibular glands, the sublingual gland has a reduced number of ducts, especially striated ducts.[2]

An imperfect muscular floor of the mouth is formed by the diaphragm of the mylohyoid muscles and the anterior bellies of the digastric muscles.[3] Herniation of tissues through a deficiency or hiatus in the mylohyoid muscle — a so-called "mylohyoid boutonniere" or "sublingual bouton" — into the submandibular area is regularly observed in dissections of cadavers.[3,4] Histologic examination of the herniated tissues, some with a size capable of clinical significance, has indicated that over 90% are salivary (sublingual, submandibular) in type.[4] A chronic sialadenitis is often observed in the herniated glands.

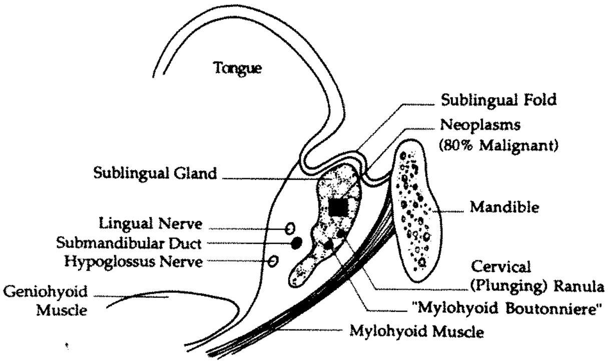

Fig 1. Diagrammatic representation of sublingual gland, its relationship to adjacent structures, and its major clinicopathologic disorders.

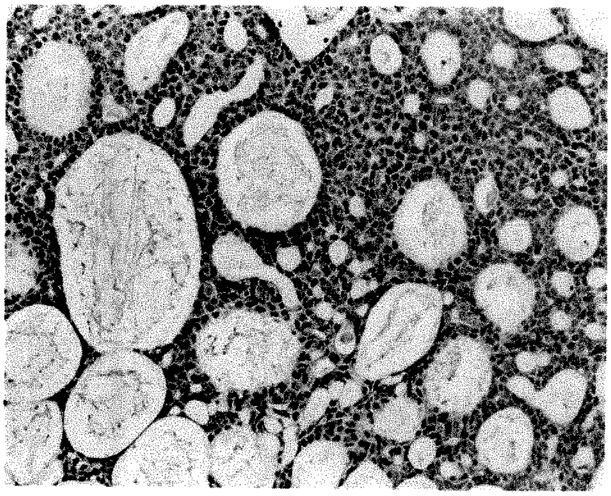

Fig 2. Adenoid cystic carcinoma, most common salivary malignancy of sublingual gland (H & E, original x100).

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.
REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

CARCINOMAS OF SUBLINGUAL GLAND
1930-1983

	Cases	
Histologic Classification	*No.*	*%*
Adenoid cystic	21	36
Mucoepidermoid	13	22
Carcinoma ex pleomorphic adenoma	9	15
Adenocarcinoma	7	12
Acinic cell	3	5
Squamous cell	1	1.7
Undifferentiated	1	1.7
Others	4	6.8
	59	100

From data presented in literature review by Nishijima et al.[6]

Neoplasms of the sublingual gland comprise only between 0.5% and 1% of all epithelial salivary gland tumors and approximately 1.5% of all carcinomas of the major salivary glands.[5] The often-observed inverse relationship between the size of a salivary gland and its incidence of malignancy is dramatically emphasized for neoplasms of sublingual gland origin: 80% versus 20% for parotid and 40% for submandibular glands. Adenoid cystic carcinoma (Fig 2) is the most frequent histologic type of carcinoma, whether in a tabulation of reported cases[6,7] (see Table[6]) or in a single institution's experience.[5]

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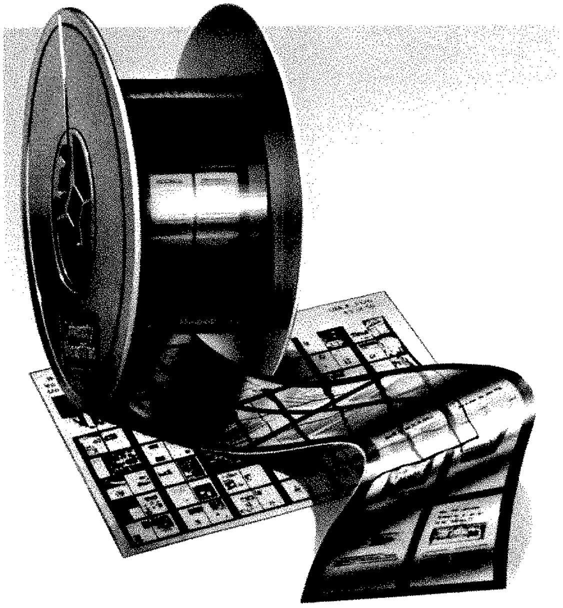

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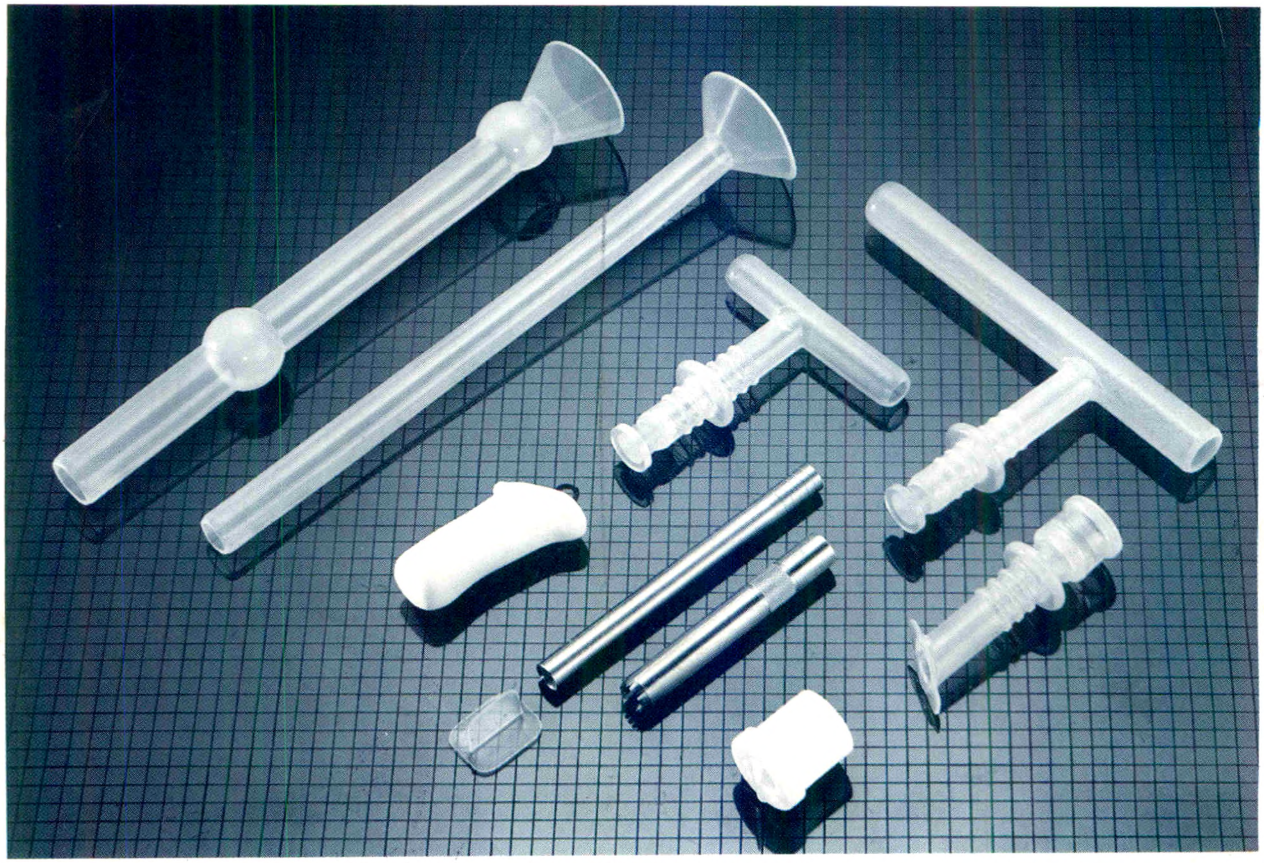

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